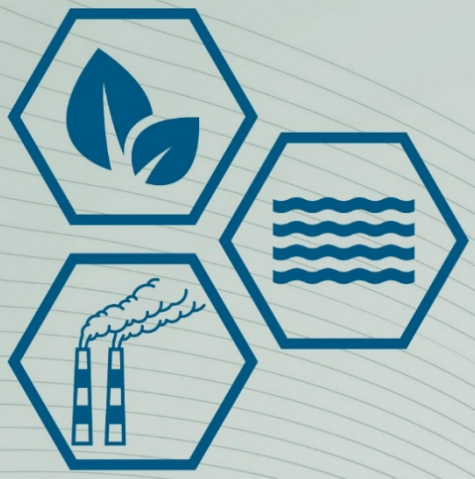


Toxicological Profile for Antimony and Compounds

Draft for Public Comment

April 2017

ATSDR
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

CS274127-A

DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

This information is distributed solely for the purpose of pre dissemination public comment under applicable information quality guidelines. It has not been formally disseminated by the Agency for Toxic Substances and Disease Registry. It does not represent and should not be construed to represent any agency determination or policy.

UPDATE STATEMENT

A Toxicological Profile for Antimony and Compounds was released in 1992. This present edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027

This page is intentionally blank.

FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 102, 1st floor, MS F-57
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (e.g.,death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.8	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.9	**Biomarkers of Exposure and Effect**
Section 3.12	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard,

Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

This page is intentionally blank.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHOR(S):

Melanie Buser, M.P.H.
Susan Zells Ingber, A.B., M.S.P.P.
Jessilynn Taylor, M.S., CDR USPHS
ATSDR, Division of Toxicology and Human Health Sciences, Atlanta, GA

Lisa Ingerman, Ph.D., D.A.B.T.
H. Danielle Johnson, B.S.
Mary Kawa, M.A.
Mario Citra, Ph.D.
SRC, Inc., North Syracuse, NY

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

This page is intentionally blank.

PEER REVIEW

A peer review panel was assembled for antimony and compounds. The panel consisted of the following members:

1. David Dorman, DVM, Ph.D., DABVT, DABT, Professor, Toxicology, School of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina;

2. Nelson Belzile, Ph.D., Full Professor, Chair, Department of Chemistry and Biochemistry, Laurentian University, Sudbury, Canada; and

3. Jeffrey L Burgess, MD, MPH, MS, Professor, Associate Dean for Research, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, Arizona.

These experts collectively have knowledge of antimony's and antimony compounds' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

This page is intentionally blank.

CONTENTS

This page is intentionally blank.

LIST OF FIGURES

This page is intentionally blank.

LIST OF TABLES

1. PUBLIC HEALTH STATEMENT FOR ANTIMONY AND COMPOUNDS

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on antimony, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. The EPA has found antimony and compounds in at least 565 of the 1,832 current or former NPL sites. The total number of NPL sites evaluated for antimony and compounds is not known. But the possibility remains that as more sites are evaluated, the sites where antimony and compounds are found may increase. This information is important because these future sites may be sources of exposure, and exposure to antimony and compounds may be harmful.

If you are exposed to antimony, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed (duration), how often you are exposed (frequency), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT IS ANTIMONY?

Antimony is a silvery white metal of medium hardness that breaks easily. Antimony is usually mixed with other metals such as lead and zinc to form mixtures of metals called alloys. These alloys are used in lead storage batteries, solder, sheet and pipe metal, bearings, castings, type metal, ammunition, and pewter. Antimony trioxide is used in the production of polyethylene terephthalate (PET) water bottles.

WHAT HAPPENS TO ANTIMONY WHEN IT ENTERS THE ENVIRONMENT?

Antimony is found in the earth's crust at about 0.2–0.3 grams per metric ton). Antimony is often found with other metals. Ores containing antimony are mined and then either changed into antimony metal or combined with oxygen to form antimony oxide. Antimony enters the environment during the mining and processing of antimony-containing ores and in the production of antimony metal, alloys, and antimony oxide, and combinations of antimony with other substances. Antimony was mined in the United States; however, the last mine closed in 2001. Impure antimony ore and metal are brought into the United States

from other countries for processing. Small amounts of antimony are released into the environment by incinerators and coal-burning power plants.

HOW MIGHT I BE EXPOSED TO ANTIMONY?

You may be exposed to antimony by breathing air, drinking water, and eating foods that contain it. You may be exposed by skin contact with soil, water, and other substances that contain antimony. You may breathe and have skin contact with high levels of antimony in dust if you live or work near antimony mines or processing companies. Children may also be exposed to antimony by eating dirt.

The amount of antimony in rivers and lakes is very low. The levels are usually less than 1 microgram per liter (µg/L). Antimony does not appear to accumulate in fish or other aquatic animals. Soil usually contains very low concentrations of antimony. Soils near mines and other work sites may contain high levels of antimony.

Food may contain small amounts of antimony. Antimony levels as high as 9.7 µg/L have been reported in drinking water. Water in PET bottles may contain higher levels of antimony.

You may also be exposed to antimony in the workplace. If you work in industries that process antimony ore and metal or make chemicals that contain antimony, such as antimony oxide, you may be exposed to antimony by breathing dust or through skin contact.

For more information on how you may be exposed to antimony, see Chapter 6.

HOW CAN ANTIMONY ENTER AND LEAVE MY BODY?

Antimony can enter your body when you drink water or eat food, soil, or other substances that contain antimony. Antimony can also enter your body if you breathe air or dust containing it. We do not know if antimony can enter your body through your skin.

When you breathe air containing antimony, antimony particles can be deposited in your lungs. Some of these particles can be coughed up and swallowed. Small particles deposited deeper in the lungs are likely to pass through the lining of the lungs and enter the bloodstream. Antimony in your lungs will enter your blood after several days or weeks, depending on the antimony compound. Less soluble compounds like antimony trioxide will stay in the lungs longer. A small amount of the antimony that you eat or drink

enters the blood after a few hours. The amount and the form of antimony in the food or water will affect how much antimony enters your blood. The amount of antimony that will enter your blood from your lungs is not known. Antimony in the blood will be distributed throughout the body, with the highest amounts in the blood, spleen, liver, and kidneys. Antimony will leave your body in feces and urine over several weeks.

Further information on how antimony enters and leaves your body is presented in Chapter 3.

HOW ANTIMONY CAN AFFECT MY HEALTH?

Antimony in the air can cause lung effects in workers and laboratory animals. Antimony can also cause heart problems. It can damage the heart muscle and cause changes in electrocardiogram (EKG) readings. High levels of antimony in drinking water can cause vomiting and abdominal pain. These effects have also been reported by antimony workers. Stomach ulcers have been seen in animals exposed to antimony in drinking water for several months. Antimony can also cause eye irritation if it gets in the eye.

Antimony can have beneficial effects when used for medical reasons. It has been used as a medicine to treat people infected with certain types of parasites. The patients typically receive a number of injections with antimony-containing compounds. Some side effects have been reported, including heart problems, nausea and vomiting, and muscle and joint pain.

Lung cancer has been observed in some studies of workers, and mice breathing high concentrations of antimony. The International Agency for Research on Cancer has determined that antimony trioxide is possibly carcinogenic to humans (group 2B) and antimony trisulfide is not classifiable as to its carcinogenicity (group 3). Antimony has not been classified for cancer effects by the Department of Health and Human Services or the EPA.

More information on how antimony can affect your health is presented in Chapters 2 and 3.

HOW CAN ANTIMONY AFFECT CHILDREN?

This section discusses potential health effects of antimony and antimony compounds exposure in humans from when they’re first conceived to 18 years of age.

We do not know if children would be more susceptible to antimony toxicity than adults. Studies in workers and in rats have shown that antimony can decreases infant growth. There is also limited information suggesting that antimony can damage the developing cardiovascular system in rats.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO ANTIMONY?

If your doctor finds that you have been exposed to significant amounts of antimony and compounds, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

Use bottled water if you have concerns about the presence of antimony in your tap water. Prevent children from eating or playing in the dirt if you live near a waste site that has been contaminated with antimony.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO ANTIMONY?

Antimony levels can be measured in urine, feces, blood, and hair. In the United States, small amounts of antimony are found in the urine of most people. High levels of antimony in the blood or urine can show that you have been recently exposed to higher than normal levels of antimony. Although these tests can show that you have been exposed to higher than normal antimony levels, they cannot be used to predict how much antimony you have been exposed to or whether the exposure will result in an adverse health effect. For more information, see Chapters 3 and 7.

WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but are not enforceable by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (e.g., an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

EPA has determined that exposure to drinking water containing 0.01 milligrams of antimony per liter (mg/L) is not expected to cause effects that are harmful to children exposed for 1 or 10 days. Lifetime exposure to drinking water containing 0.006 mg/L is not likely to cause adverse health effects.

OSHA has set a limit of 0.5 mg/m^3 of antimony in workroom air to protect workers during an 8-hour work shift (40-hour workweek). NIOSH also recommends that the concentration in workroom air be limited to 0.5 mg/m^3 for antimony and for stibine (antimony hydride) averaged over an 8-hour work shift. Further information on regulations and guidelines pertaining to antimony is provided in Chapter 8.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. You may also contact your doctor if experiencing adverse health effects or for medical concerns or questions. ATSDR can also provide publicly available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO ANTIMONY AND COMPOUNDS IN THE UNITED STATES

Antimony is naturally present in the earth's crust at levels of about 0.2–0.3 mg/kg (ppm), but these levels vary by location. It can be transported into streams and waterways from natural weathering of soil, as well as from anthropogenic sources. Antimony enters the environment during the mining and processing of antimony-containing ores and in the production of antimony metal, alloys, antimony oxide, and combinations of antimony with other substances. Antimony was mined in the United States; however, the last mine closed in 2001. Impure antimony ore and metal are imported into the United States from other countries for processing. Small amounts of antimony are released into the environment by incinerators and coal-burning power plants. Studies indicate that antimony is retained in the soil through adsorption and can sorb onto clay minerals, oxides, and hydroxides in the soil and aquatic sediment.

Antimony is predominantly in the +5 oxidation state in both aerobic freshwater and seawater. These waters also contain antimony in the +3 oxidation state to a lesser extent. Trivalent antimony is the dominant oxidation state of antimony in anaerobic environments. The predominant trivalent species in the environment is antimony trihydroxide ($Sb(OH)_3$) and the predominant pentavalent species is hexahydroxoantimonate ($Sb(OH)_6^-$), as predicted by thermodynamic calculations.

Antimony can be reduced and methylated by microorganisms in anaerobic sediment, releasing volatile methylated antimony compounds into the water. Multiple microorganisms have been found to methylate antimony in the soil and water and other anaerobic environments.

The general population is exposed to low levels of antimony from ingestion of food and drinking water and possibly by inhalation of particulate matter containing antimony in ambient air. Occupational exposures of antimony may occur at smelters, coal-fired plants, and refuse incinerators that process or release antimony.

2.2 SUMMARY OF HEALTH EFFECTS

Antimony and its compounds are among the oldest known remedies in the practice of medicine and they have been used to treat a variety of illnesses over the last 600 years. Currently, antimony compounds are used to treat the parasitic disease leishmaniasis. Toxic side effects in humans following intraperitoneal,

intravenous, or intramuscular injection of an antimony-containing drug have been reported, including altered electrocardiograms (EKGs), vomiting, diarrhea, and joint and/or muscle pain. These side effects are more frequently observed following administration of trivalent antimony compounds, especially antimony potassium tartrate or antimony sodium tartrate; side effects have also been found in humans administered pentavalent organic compounds such as sodium antimony gluconate or meglumine antimoniate.

Adverse health effects have also been observed in humans and animals following inhalation, oral, or dermal exposure to antimony and antimony compounds. These studies predominantly assessed the toxicity of trivalent antimony compounds, particularly antimony trioxide and antimony potassium tartrate. In both humans and animals, the respiratory tract is the predominant target of antimony toxicity following inhalation exposure, and a systematic review of the data (see Appendix B for additional information) supports the conclusion that antimony is presumed to cause respiratory health effects in humans. The lung is the primary target of toxicity within the respiratory tract, and effects are observed following acute-, intermediate-, and chronic-duration exposure. In antimony workers, pneumoconiosis and clinical signs such as coughing and laryngitis have been reported. A relationship between exposure level and effect cannot be established from these data because the workers were also exposed to other compounds, including arsenic oxide, iron oxide, hydrogen chloride, and hydrogen sulfide. In laboratory animals, the lung effects include the accumulation of antimony particles in the lungs, increases in alveolar/intra-alveolar macrophages, decreases in antimony lung clearance times, chronic interstitial inflammation, and interstitial fibrosis. Lung effects have been found in rats, mice, and rabbits following exposure to antimony trioxide, antimony trisulfide, and antimony ore; lung effects have also been observed in laboratory animals following exposure to stibine gas. Intermediate- and chronic-duration studies demonstrated that pulmonary damage can occur postexposure due to the persistence of the antimony trioxide in the lung. At the end of a 13-week or 1-year exposure to antimony trioxide, histological alterations in the lungs were limited to increases in alveolar/intra-alveolar macrophages; however, after 27-week or 1-year recovery periods, respectively, interstitial inflammation and fibrosis were observed. Other respiratory effects that have been observed in some studies include squamous metaplasia of the epiglottis and hyperplasia of the nasal respiratory epithelium. The lowest lowest-observed-adverse-effect levels (LOAELs) for respiratory tract effects following acute-, intermediate-, and chronic-duration exposures are 12 mg Sb/m^3 as antimony trioxide, 4.11 mg Sb/m^3 as antimony trioxide, and 1.6 mg Sb/m^3 as antimony trioxide, respectively.

Cardiovascular effects, especially myocardial damage and alterations in EKGs, have been observed in humans and animals exposed to antimony. Based on the systematic review of the available data (Appendix B), ATSDR concluded that antimony is suspected to cause cardiovascular health effects, specifically myocardial and EKG alterations, in humans. In workers exposed to antimony trisulfide dust, EKG alterations were found in about 50% of the workers. A small number of animal studies included EKG readings; these studies reported alterations in rats, rabbits, and dogs exposed to airborne antimony trisulfide. No alterations were observed in guinea pigs or pigs exposed to airborne antimony trioxide for intermediate or chronic durations. These findings are supported by reports of altered EKG readings (particularly prolongation of the QT interval) in individuals exposed to repeated injections of antimony and in experimental studies in laboratory animals injected with trivalent or pentavalent antimony compounds.

Historically, antimony has been known for its emetic properties. Gastrointestinal tract irritation is a presumed health effect of antimony in humans based on the systematic review of occupational exposure studies and inhalation and oral exposure studies in laboratory animals. Abdominal pain, vomiting, nausea, and ulcers have been observed in antimony workers. Gastrointestinal effects have also been observed in humans receiving intramuscular injections of antimony. Vomiting has also been observed in dogs following acute oral exposure and chronic inflammation and/or ulceration was observed in the forestomach of mice following acute oral exposure to antimony potassium tartrate or chronic inhalation exposure to antimony trioxide. Overt signs of gastrointestinal irritation or histological alterations of the gastrointestinal tract have not been observed in numerous inhalation or oral exposure studies in rats.

There are some data to indicate that antimony decreases blood glucose levels following intermediate or chronic oral exposure in rats, with supporting data from an intermediate-duration study finding decreased blood glucose levels in rats administered intramuscular injections of organic pentavalent compounds. Based on the systematic review, it was categorized as a suspected health effect in humans.

The developmental toxicity of antimony has not been extensively evaluated in humans or animals. Decreases in growth have been reported in the infants of female antimony workers; interpretation of the results of this study is limited by the lack of study details, particularly regarding the control group, antimony concentrations in the facility, type of work the women performed, and potential exposure to other compounds. Studies in animals support the findings of this occupational exposure study. Decreases in pup growth were observed in the offspring of rats orally exposed to antimony trichloride during gestation and lactation, and decreases in birth weight or fetal weight were observed in rats administered

organic pentavalent antimony compounds via subcutaneous or intramuscular injection or administered antimony trichloride via intramuscular injection. Antimony does not appear to result in external or skeletal abnormalities in rats following oral or parenteral administration. Based on these data, developmental toxicity is a suspected human health effect (see Appendix B for additional information). Exposure to antimony during gestation and/or lactation and post-weaning exposure has resulted in impaired vasomotor response to 1-noradrenaline, 1-isoprenaline, and acetylcholine in 30- and 60-day-old rat pups.

Other health effects that have been observed in animals orally exposed to higher doses of antimony include hepatocellular vacuolization, hematological alterations including decreases in red blood cell counts and hemoglobin levels, and histological alterations in the thyroid.

Dermatosis and ocular irritation have been reported in workers exposed to airborne antimony. The dermatitis was seen more often during the summer months and in workers exposed to high temperatures. It is probably the result of antimony being dissolved in sweat and penetrating the sweat glands. In general, dermal effects have not been observed in animal studies. Animal studies do provide support for antimony being considered an ocular irritant. Eye irritation has been reported in animals exposed to stibine gas and following instillation of antimony thioantimonate into rabbit eyes. Additionally, increases in corneal opacities and cataracts have been observed in animals repeatedly exposed to airborne antimony trioxide.

Two occupational exposure studies examining carcinogenicity of antimony have found increases in lung cancer deaths. Mixed results have been found in chronic inhalation studies in rats. Increases in lung neoplasms were observed in rats exposed to 4.2 or 36 mg Sb/m^3 as antimony trioxide for approximately 1 year. A third 1-year exposure study (followed by a 1-year recovery) did not find lung neoplasms in rats exposed to 3.8 mg Sb/m^3. A 2-year inhalation study conducted by the National Toxicology Program found increases in the incidence of alveolar/bronchiolar adenomas in rats and alveolar/bronchiolar adenomas and carcinomas in mice. No increases in tumors were found in rats or mice following lifetime oral exposure to antimony potassium tartrate. The International Agency for Research on Cancer categorized antimony trioxide in group 2B (possibly carcinogenic to humans) and antimony trisulfide in group 3 (not classifiable as to its carcinogenicity to humans). The NTP and EPA have not classified the carcinogenicity of antimony.

2.3 MINIMAL RISK LEVELS (MRLs)

As summarized in Table 2-1, inhalation MRLs have been derived for acute-, intermediate-, and chronic-duration exposure to antimony and oral MRLs have been derived for acute- and intermediate-duration exposure to antimony. Refer to Section 3.6.2 and Appendix A for detailed information regarding MRL derivation.

Table 2-1. Minimal Risk Levels (MRLs) for Antimony[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure					
Acute	0.001 mg Sb/m^3	Squamous metaplasia of the epiglottis of mice exposed to ≥12 mg Sb/m^3	$BMCL_{HEC}$ of 0.035 mg Sb/m^3	30[b]	NTP 2016
Intermediate	Adopted the acute-duration inhalation MRL of 0.001 mg Sb/m^3				
Chronic	0.0003 mg Sb/m^3	Chronic lung inflammation in female rats	$BMCL_{HEC}$ of 0.008 mg Sb/m^3	30[b]	Newton et al. 1994
Oral exposure					
Acute	1 mg Sb/kg/day	Focal ulceration of the forestomach in mice	NOAEL of 99 mg Sb/kg/day	100[c]	NTP 1992
Intermediate	0.0006 mg Sb/kg/day	Decreased serum glucose levels in female rats	NOAEL of 0.064 mg Sb/kg/day	100[c]	Poon et al. 1998
Chronic	Insufficient data for derivation of an MRL				

[a]The respective exposure durations for acute, intermediate, and chronic MRLs are ≤14 days, 15–364 days, and ≥1 year.
[b]Uncertainty factors: 3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability.
[c]Uncertainty factors: 10 for extrapolation from animals to humans and 10 for human variability.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; LOAEL = lowest observed adverse effect level

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of antimony and compounds. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

Studies in which humans or animals are exposed to various antimony compounds are discussed in this chapter. The antimony compounds include organic forms (antimony potassium tartrate, antimony sodium tartrate, antimony acetate), inorganic trivalent antimony (antimony trioxide, antimony trichloride, antimony trisulfide, stibine), inorganic pentavalent antimony (antimony pentoxide, antimony pentasulfide), antimony-containing drugs (stibocaptate, stibophen, meglumine), and metallic antimony. No limitations were placed on the selection of compounds for inclusion in this toxicological profile. Most of the available data evaluated the toxicity of trivalent antimony, in particular antimony trioxide.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (e.g., death, systemic, immunological, neurological, reproductive, developmental, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a

considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of antimony are indicated in Table 3-1 and Figure 3-1.

A User's Guide has been provided at the end of this profile (see Appendix C). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Health effects have been observed in humans and animals following inhalation exposure to several antimony compounds. Health effects following exposure to airborne stibine (antimony hydride), antimony trisulfide, antimony ore, antimony trioxide, antimony pentoxide, antimony trichloride, antimony pentasulfide, and metallic antimony are discussed below. Of these, stibine is a naturally occurring gas; for ease of comparison, its concentrations will be expressed in units of mg/m^3 (1 ppm stibine = 5.1 mg/m^3).

In the previous version of the toxicological profile for antimony (ATSDR 1992) and in other documents, intermediate- and chronic-duration studies conducted in rats exposed to antimony trioxide were cited as unpublished reports (Bio/Dynamics 1985, 1990); these studies have subsequently been published as Newton et al. (1994). Unless data are unique to the unpublished version of the studies, data from these studies will be cited to Newton et al. (1994). Additionally, data from the Groth et al. (1986) chronic rat study of antimony trioxide and antimony ore were also cited as an unpublished report (Wong et al. 1979); to avoid confusion that these are separate studies, the data will be cited only to Groth et al. (1986).

3.2.1.1 Death

No studies were located regarding death in humans after inhalation exposure to antimony.

Deaths occurred in guinea pigs exposed to approximately 37.9 mg antimony/m^3 as antimony trioxide dust for approximately 60–178 days (Dernehl et al. 1945) and in guinea pigs and rats exposed to 1,395 mg antimony/m^3 as stibine gas for 30 minutes (Price et al. 1979). Pulmonary edema was a contributing factor to the death of rats and guinea pigs exposed to stibine (Price et al. 1979). None of the rats or guinea pigs exposed to ≤799 mg antimony/m^3 for 30 minutes died (Price et al. 1979). Lower concentrations of antimony trisulfide (84–105 mg antimony/m^3), antimony trioxide (≥36 mg antimony/m^3), or antimony ore (17.5 mg antimony/m^3) did not affect the survival of rats exposed for approximately 1 year (Gross et al. 1952; Groth et al. 1986; Newton et al. 1994; Watt 1983). However, a 2-year exposure to ≥8.3 mg Sb/m^3 as antimony trioxide resulted in decreased survival in female rats and male and female mice (NTP 2016). The decreased survival was attributed to lung inflammation and/or lung carcinomas (mice only).

The LOAEL values for death in animals exposed to stibine or antimony trioxide are presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for each systemic effect in each species and duration are presented in Table 3-1 and plotted in Figure 3-1. Summaries of systemic effects in humans are presented in Table 3-2.

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
ACUTE EXPOSURE									
Death									
1	Guinea Pig (Hartley) 5M, 5F	30 minutes; 0, 122, 799, 1,395	CS, BW, HP				1395	Increased mortality (8/10) at an unspecified time post-exposure.	Price et al. 1979 (stibine)
2	Rat (Sprague Dawley) 5M, 5F	30 minutes; 0, 122, 799, 1,395	CS, BW, GN, HP				1395	Increased mortality (7/10) at an unspecified time post-exposure.	Price et al. 1979 (stibine)
Systemic Effects									
3	Rat (Sprague Dawley) 5M, 5F	30 minutes; 0, 122, 799, 1,395	CS, BW, GN, HP	Resp Cardio Hepatic Renal Endocr Bd Wt	122 122 122 122 122 122	1395		Pulmonary edema and congestion were observed at 1395 mg Sb/m^3.	Price et al. 1979 (stibine)
4	Rat (Wistar Han) 5M, 5F	6 hours/day 5 days/week 16 days; 0, 3.1, 6.3, 12, 25, 50 mg	CS, BW, OW, GN, HP	Resp Bd Wt	12 50	25		Chronic inflammation in the lungs at ≥25 mg Sb/m^3; increase in squamous metaplasia in the epiglottis at ≥25 mg Sb/m^3.	NTP 2016 (antimony trioxide)
5	Mouse (B6C3F1) 5M, 5F	6 hours/day 5 days/week 17 days; 0, 3.1, 6.3, 12, 25, 50	CS, BW, OW, GN, HP	Resp Bd Wt	6.3[b] 50	12		Squamous metaplasia in epiglottis epithelium at 12 mg Sb/m^3; increases in relative lung weights at ≥ 3.1 mg Sb/m^3.	NTP 2016 (antimony trioxide)
6	Rabbit (NS) 5M, 5F	7 hours/day 5 days; 0 or 19.9	LE, OF, HP	Resp Cardio Hepatic Renal 19.9		19.9 19.9 19.9		Degenerative changes in the heart, liver, and kidneys, and inflammation of the lungs were observed. Morphological changes in heart tissue were accompanied by alterations in the EKG. Only qualitative data were presented.	Brieger et al. 1954 (antimony trisulfide)
7	Guinea Pig (Hartley) 5M, 5F	30 minutes; 0, 122, 799, 1,395	CS, BW, GN, HP	Resp Renal	799 122	1395 799		Pulmonary edema and congestion at 1395 mg Sb/m^3; investigators did not report whether pulmonary effects were observed in controls. Renal tubular dilation in 3/10 animals at 799 mg Sb/m^3; investigators did not report whether renal lesions occurred at 1395 mg Sb/m^3.	Price et al. 1979 (stibine)

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
INTERMEDIATE EXPOSURE									
Systemic Effects									
8	Rat (Fischer 344) 50M, 50F	6 hours/day 5 days/week 13 weeks; 0, 0.21, 0.902, 4.11, 19.60	CS, BW, OP, HE, BI, HP	Resp Cardio Hemato Bd Wt	0.902 19.60 19.60 19.60	4.11	At	≥4.11 mg Sb/m^3, increases in alveolar/intraalveolar macrophages, increases in relative lung weight, and increases in lung clearance half-times were observed. Increased incidences of chronic interstitial inflammation and fibrosis were observed at 19.60 mg Sb/m^3 in the lungs at the end of a 27-week recovery period.	Newton et al. 1994 (antimony trioxide)
9	Rat (NS) 10 (controls), 24 (exposed)	4 hours/day 1.5-2 months; 0, 209	MX, DX, BW, GN, HP, OF	Resp Hepatic Renal Endocr Bd Wt	 209	209 209 209 209		Unspecified pathological changes in the lungs, liver, kidneys, and pancreas; only qualitative data were provided.	Belyaeva 1967 (antimony trioxide)
10	Rat (Wistar) 10M	7 hours/day 5 days/week 6 weeks; 0, 2.20	LE, CS, BW, OF, GN, HP	Resp Cardio Bd Wt	 2.20	2.20 2.20		Altered EKG and microscopic changes in heart muscle consistent with degeneration of the myocardium and mild congestion and focal hemorrhages in the lungs.	Brieger et al. 1954 (antimony trisulfide)
11	Dog (NS) 2F	7 hours/day 5 days/week 7 weeks; 0, 3.81	LE, CS, BW, HE, BI	Cardio Hemato Bd Wt	3.81 3.81 3.81			Occasional swelling of myocardial fibers, but no consistent changes in the EKG.	Brieger et al. 1954 (antimony trisulfide)
12	Dog (NS) 2F	7 hours/day 5 days/week 10 weeks; 0, 3.98	LE, CS, BW, HE, BI	Cardio Hemato Bd Wt	 3.98 3.98	3.98		EKG changes indicative of myocardial injury; occasional swelling of myocardial fibers.	Brieger et al. 1954 (antimony trisulfide)
13	Rabbit (NS) 6M	7 hours/day 5 days/week 6 weeks; 0, 4.02	LE, HE, BI, OF, GN, HP	Cardio Hemato Hepatic Renal	 4.02 4.02 4.02	4.02		Altered EKG, heart enlargement, swelling of myocardial fibers; only qualitative data were presented.	Brieger et al. 1954 (antimony trisulfide)
14	Guinea pig 24NR (NS)	2 hours/day 7 days/week 2 weeks 3 hours/day 7 days/week 30 weeks 0, 37.9	CS, BW, HE, OF, HP	Resp Hemato Hepatic	 37.9	37.9 37.9		Pneumonitis, decreases in total and differential leukocyte counts, fatty degeneration in the liver, and hypertrophy of lymphoid follicles in the spleen were observed.	Dernehl et al. 1945 (antimony trioxide)

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
Reproductive Effects									
15	Rat (NS) 10 (controls), 24 (exposed)	4 hours/day 1.5-2 months; 0, 209	MX, DX, BW, GN, HP, OF			209		Reduced fertility (16/24 conceived compared to 10/10 in controls) and histological alterations in reproductive organs; only qualitative data were presented.	Belyaeva 1967 (antimony trioxide)
Developmental Effects									
16	Rat (NS) 10 (controls), 24 (exposed)	4 hours/day 1.5-2 months; 0, 209	MX, DX, BW, GN, HP, OF			209		Reduced litter size; it is unknown if this was due to pre-implantation loss or post-implantation loss.	Belyaeva 1967 (antimony trisulfide)
CHRONIC EXPOSURE									
Death									
17	Rat (Wistar Han) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP				8.3	Decreased survival in females at ≥8.3 mg Sb/m^3; significant trend for decreases in survival in males.	NTP 2016 (antimony trioxide)
18	Mouse (B6C3F1) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP				8.3	Decreases in survival at ≥8.3 mg Sb/m^3.	NTP 2016 (antimony trioxide)
Systemic Effects									
19	Rat (Fisher 344) 65M, 65F	6 hours/day 5 days/week 12 months; 0, 0.05, 0.43, 3.8	CS, BW, OP, HE, BI, HP	Resp Cardio Hemato Ocular Bd Wt	0.05[c] 3.8 3.8 0.05 3.8	0.43 0.43 		Moderate or severe lenticular degeneration was observed at 3.8 mg Sb/m^3. An increase in alveolar/intraalveolar macrophages were observed in all antimony groups. An increase in chronic interstitial inflammation was observed in rats exposed to 0.43 (females only) and 3.8 mg Sb/m^3 and terminated during the recovery period. An 80% decrease in lung clearance was observed at 3.8 mg Sb/m^3.	Newton et al. 1994 (antimony trioxide)
20	Rat (Sprague-Dawley) 50M	25 hours/week 14.5 months; 0, 84-105	GN, HP	Resp		84		Gross and microscopic alterations in the lungs consistent with lipoid pneumonia.	Gross et al. 1952 (antimony trisulfide)

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
21	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0, 36	LE, CS, BW, GN, HP	Resp Cardio Gastro Hepatic Renal Endocr Bd Wt Other (pancreas, bladder)	 36 36 36 36 36 36 36	36		Interstitial fibrosis and alveolar-wall cell hypertrophy and hyperplasia which persisted after exposure termination.	Groth et al. 1986 (antimony trioxide)
22	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0, 17.5	LE, CS, BW, GN, HP	Resp Cardio Gastro Hepatic Renal Endocr Bd Wt Other (pancreas, bladder	 17.5 17.5 17.5 17.5 17.5 17.5 17.5	17.5		Interstitial fibrosis and alveolar-wall cell hypertrophy and hyperplasia which persisted after exposure termination.	Groth et al. 1986 (antimony ore)
23	Rat (Fischer 344) 49-50F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP	Resp Cardio Gastro Musc/Skel Hepatic Renal Endocr Bd Wt Metab Other (pancreas)	 4.2 4.2 4.2 4.2 4.2 4.2 4.2 4.2 4.2	1.6		Focal fibrosis, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumocyte hyperplasia, and pigmented macrophages in lungs. Incidence of lesions is time and exposure concentration-related.	Watt 1983 (antimony trioxide)

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
24	Rat (Wistar Han) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP	Resp		2.5		**Respiratory:** inflammation, proteinosis, hyperplasia, and fibrosis at ≥2.5 mg Sb/m^3; hyperplasia of nasal respiratory epithelium at 2.5 mg Sb/m^3 (males only) and 25 mg Sb/m^3 (males and females) and squamous metaplasia of nasal epithelium in males at 25 mg Sb/m^3; **Musculoskeletal**: bone marrow hyperplasia at 25 mg Sb/m^3; **Cardiovascular:** chronic inflammation of muscular arteries at 8.3 (females only) and 25 mg Sb/m^3; **Renal**: hyaline droplet accumulation at 8.3 (females only) and 25 mg Sb/m^3 and nephropathy in females at 25 mg Sb.m^3; **Body weight:** decreases in body weight gain in females at 2.5 (10%), 8.3 (20%), and 25 (28%) mg Sb/m^3 and in males at 25 mg Sb/m^3 (20%); **Ocular:** ciliary body inflammation at 25 mg Sb/m^3 and retinal atrophy in females at ≥2.5 mg Sb/m^3.	NTP 2016 (antimony trioxide)
				Cardio	2.5	8.3			
				Gastro	25				
				Musculoskel	8.3	25			
				Hepatic	25				
				Renal	2.5	8.3			
				Endocrine	25				
				Ocular		2.5			
				Bd Wt	2.5	8.3			
25	Mouse (B6C3F1) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP	Resp		2.5		**Respiratory:** chronic, inflammation, fibrosis (alveolus and pleural), and alveolar and bronchiolar epithelial hyperplasia at ≥2.5 mg Sb/m^3; laryngeal respiratory epithelial hyperplasia were observed at ≥8.3 mg Sb/m^3; squamous metaplasia of nasal respiratory epithelium in females at 25 mg Sb/m^3; and epithelial hyperplasia in the trachea of males exposed to 25 mg Sb/m^3. **Hematological:** hematopoietic cell proliferation in the spleen in females at 25 mg Sb/m^3. **Cardiovascular:** chronic inflammation of epicardium at ≥8.3 mg Sb/m^3. **Gastrointestinal:** chronic active inflammation in the forestomach of males at 25 mg Sb/m^3. **Musculoskeletal:** bone marrow hyperplasia at ≥2.5 mg Sb/m^3. **Body weight:** decreases in body weight gain in males at 8.3 and 25 mg Sb/m^3 (11 and 25%) and in females at 25 mg Sb/m^3 (21%).	NTP 2016 (antimony trioxide)
				Cardio	2.5	8.3			
				Gastro	8.3	25			
				Musculoskel		2.5			
				Hepatic	25				
				Renal	25				
				Endocrine	25				
				Bd Wt	2.5	8.3			

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
26	Pig (Sinclair S-1 miniature pig) 2-3F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP	Resp Cardio Gastro Musc/Skel Hepatic Renal Endocr Bd Wt Other (pancreas)	4.2 4.2 4.2 4.2 4.2 4.2 4.2 4.2 4.2			No histological alterations were observed.	Watt 1983 (antimony trioxide)
Immuno/Lymphoret									
27	Rat (Fisher 344) 65 M, 65 F	6 hours/day 5 days/week 12 months; 0, 0.05, 0.43, 3.8	LE, CS, BW, HP, OP, GN, OW, HP		0.43	3.8		Increased incidence of reticuloendothelial cell hyperplasia in peribronchiolar lymph nodes; no tests of immunocompetence were conducted in the study.	Newton et al. 1994 (antimony trioxide)
28	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0, 36	LE, CS, BW, GN, HP		36			No histological alterations in spleen or lymph nodes.	Groth et al. 1986 (antimony trioxide)
29	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0 ,17.5	LE, CS, BW, GN, HP			17.5		Mononuclear cell granulomas in tracheobronchial lymph nodes.	Groth et al. 1986 (antimony ore)
30	Rat (Fischer 344) 49-50F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP		4.2			No histological alterations in the thymus or lymph nodes.	Watt 1983 (antimony trioxide)
31	Rat (Wistar Han) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP			2.5		Lymphoid hyperplasia in bronchial and mediastinal lymph nodes at ≥2.5 mg Sb/m^3.	NTP 2016 (antimony trioxide)
32	Mouse (B6C3F1) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP			2.5		Lymphoid hyperplasia in the bronchial and mediastinal (males only) lymph nodes and thymic cellular depletion at ≥2.5 mg Sb/m^3.	NTP 2016 (antimony trioxide)
33	Pig (Sinclair S-1 miniature pig) 2-3F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2			4.2			No histological alterations in the thymus or lymph nodes.	Watt 1983 (antimony trioxide)

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
Neurological Effects									
34	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0, 36	LE, CS, BW, GN, HP		36			No histological alterations in the brain.	Groth et al. 1986 (antimony trioxide)
35	Rat (Fischer 344) 49-50F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2 mg	CS, LE, BW, OW, HE, BI, GN, HP		4.2			No histological alterations in the brain.	Watt 1983 (antimony trioxide)
36	Rat (Wistar Han) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP		25			No histological alterations were observed in the brain.	NTP 2016 (antimony trioxide)
37	Mouse (B6C3F1) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP		25			No histological alterations were observed in the brain.	NTP 2016 (antimony trioxide)
38	Pig (Sinclair S-1 miniature pig) 2-3 F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP		4.2			No histological alterations in the brain.	Watt 1983 (antimony trioxide)
Reproductive Effects									
39	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0, 36	LE, CS, BW, GN, HP		36			No histological alterations were observed in reproductive tissues.	Groth et al. 1986 (antimony trioxide)
40	Rat (Wistar) 90M, 90F;	7 hours/day 5 days/week 52 weeks; 0, 17.5	LE, CS, BW, GN, HP		17.5			No histological alterations in reproductive tissues.	Groth et al. 1986 (antimony ore)
41	Rat (Fischer 344) 49-50F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP		4.2			Exposure to antimony trioxide dusts did not significantly affect the gross or microscopic appearance of the ovaries and uterus.	Watt 1983 (antimony trioxide)
42	Rat (Wistar Han) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP			2.5		An increase in epithelial hyperplasia of the prostate gland was observed in 2.5 and 8.3 mg Sb/m^3; increases in severity were observed in all antimony exposed groups.	NTP 2016 (antimony trioxide)

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
43	Mouse (B6C3F1) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP		25			No histological alterations were observed in reproductive tissues.	NTP 2016 (antimony trioxide)
44	Pig (Sinclair S-1 miniature pig) 2-3F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2	CS, LE, BW, OW, HE, BI, GN, HP		4.2			Exposure to antimony trioxide dusts did not significantly affect the gross or microscopic appearance of the ovaries and uterus.	Watt 1983 (antimony trioxide)
Cancer									
45	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0, 36	LE, CS, BW, GN, HP				36	Increased incidence of lung neoplasms in females.	Groth et al. 1986 (antimony trioxide)
46	Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks; 0, 17.5	LE, CS, BW, GN, HP				17.5	Increased incidence of lung neoplasms in females.	Groth et al. 1986 (antimony ore)
47	Rat (Fischer 344) 49-50F	6 hours/day 5 days/week 55 weeks; 0, 1.6, 4.2					4.2	Increase in lung neoplasms.	Watt 1983 (antimony trioxide)
48	Rat (Wistar Han) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP				8.3	Alveolar/bronchiolar adenomas in females at ≥8.3 mg Sb/m^3, benign pheochromocytoma in adrenal medulla at 25 mg Sb/m^3, and combined incidence of benign and malignant pheochromocytomas in females at 25 mgSb/m^3.	NTP 2016 (antimony trioxide)

Table 3-1. Levels of Significant Exposure to Antimony – Inhalation

Figure key[a]	Species (strain) No./group	Exposure duration/ Concentrations (mg Sb/m^3)	Parameters monitored	System	NOAEL (mg/m^3)	Less serious LOAEL (mg/m^3)	Serious LOAEL (mg/m^3)	Results	Reference/comments
49	Mouse (B6C3F1) 50M, 50F	6 hours/day 5 days/week 2 years; 0, 2.5, 8.3, 25	CS, LE, BW, GN, HP				2.5	Increased incidences of alveolar/bronchiolar adenomas, carcinomas, or combined were observed at ≥2.5 mg Sb/m^3. Other neoplastic lesions included malignant lymphoma in females at ≥2.5 mg Sb/m^3 and fibrous histiocytoma in the skin in males at 25 mg Sb/m^3.	NTP 2016 (antimony trioxide)

[a]The number corresponds to entries in Figure 3-1.
[b]Used to derive an acute-duration inhalation MRL of 0.001 mg Sb/m^3 calculated using benchmark dose analysis. The $BMCL_{10}$ of 0.94 mg Sb/m^3 was adjusted for intermittent exposure (6 hours/day, 5 days/week), multiplied by the RDDR of 0.206, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).
[c]Used to derive a chronic-duration inhalation MRL of 0.0003 mg Sb/m^3. The $BMCL_{10}$ of 0.10 mg Sb/m^3 was adjusted for intermittent exposure (6 hours/day, 5 days/week), multiplied by the RDDR of 0.436, and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Parameters monitored: BI = biochemical changes; BW = body weight; CS= clinical signs; DX = developmental toxicity; GN = gross necropsy; HE = hematology; HP = histopathology; LE = lethality; MX = maternal toxicity; OF = organ function; OP = ophthalmology; OW = organ weight

Bd wt = body weight; BMCL = lower 95% confidence limit on the benchmark concentrations; Cardio = cardiovascular; EKG = electrocardiogram; Endocr = endocrine; F = female(s); Gastro = gastrointestinal; Hemato = hematological; M = male(s); metab = metabolic; MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; NS = not specified; Resp = respiratory; Sb = antimony

Figure 3-1. Levels of Significant Exposure to Antimony - Inhalation

Acute (≤14 days)

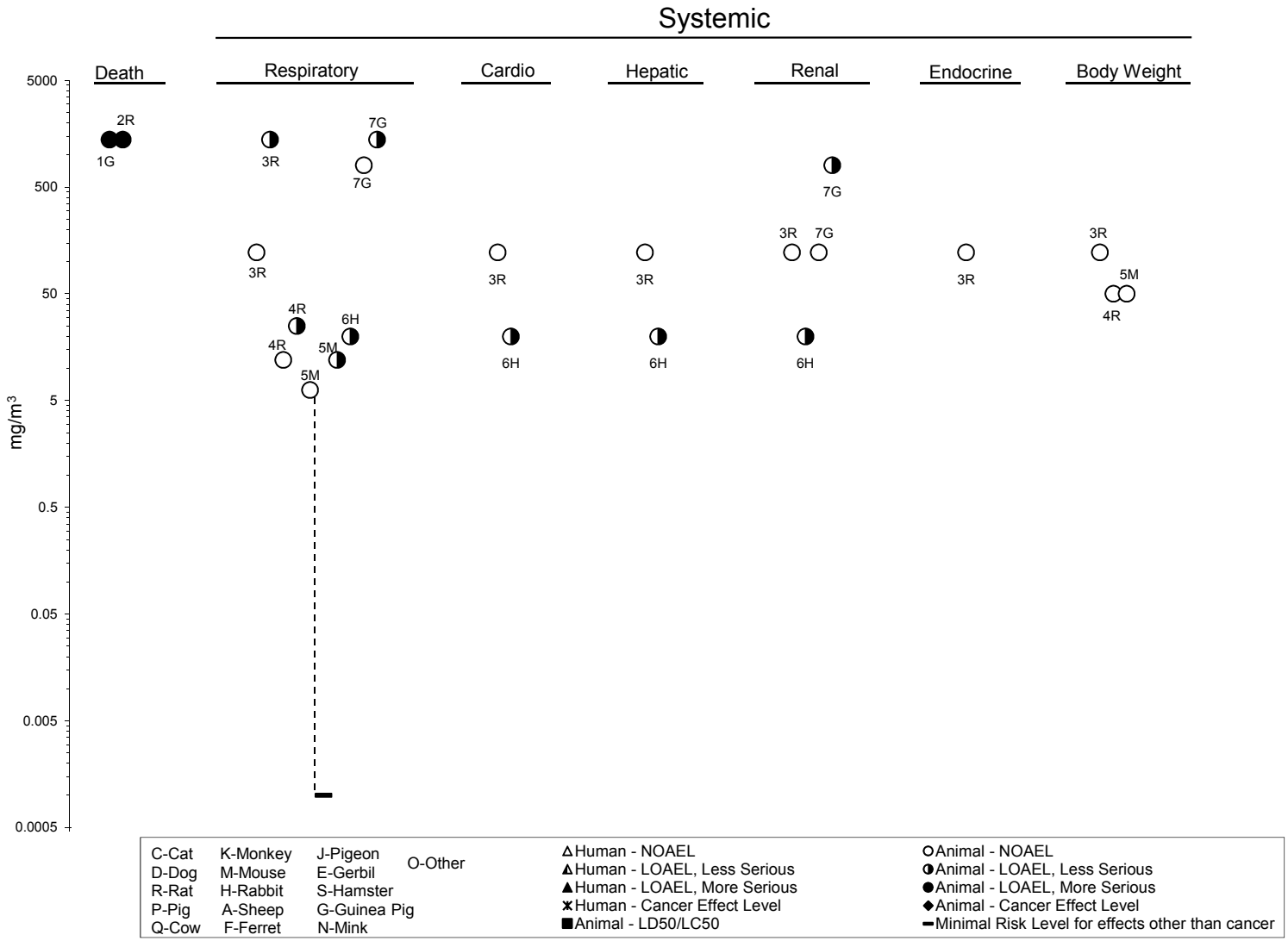


Figure 3-1. Levels of Significant Exposure to Antimony - Inhalation *(Continued)*

Intermediate (15-364 days)

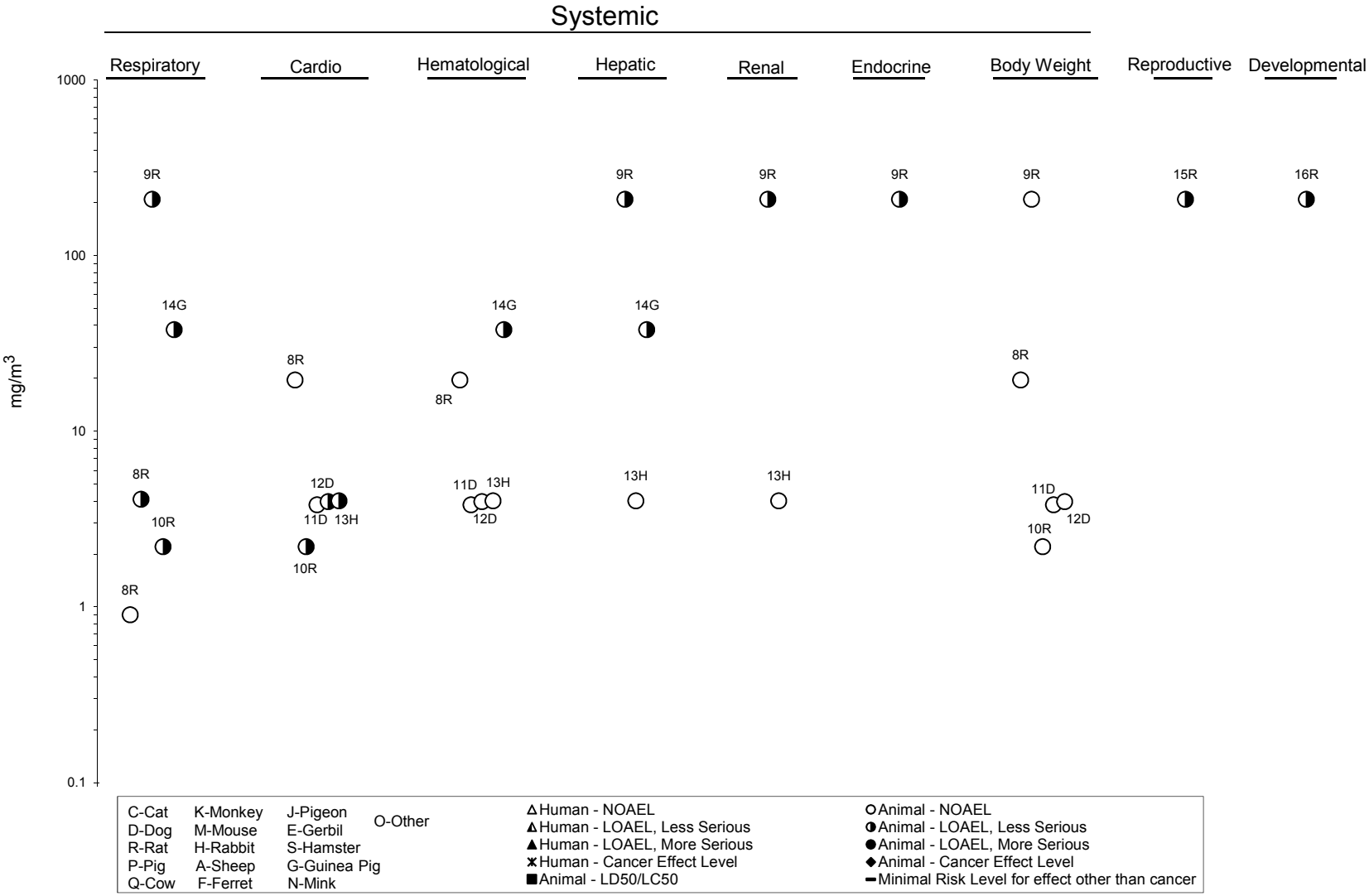


Figure 3-1. Levels of Significant Exposure to Antimony - Inhalation *(Continued)*

Chronic (≥365 days)

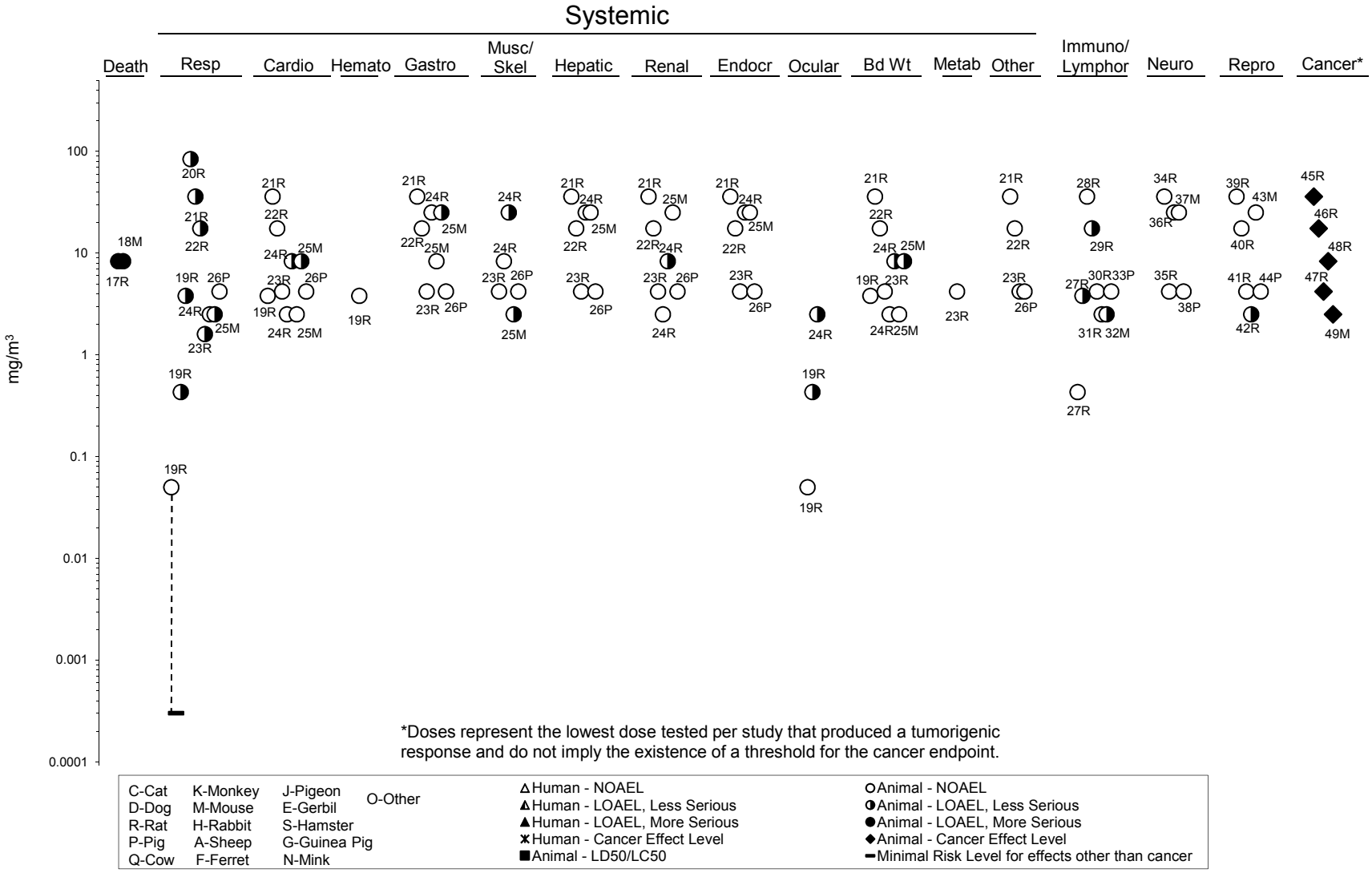


Table 3-2. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Belyaeva 1967	Female workers at an antimony metallurgical facility; some of the women worked in a more dusty section of the facility. A control group was also examined; however, no information was provided whether the controls were matched to the exposed group or whether they had similar jobs without antimony exposure. The number of subjects was not reported; antimony levels were measured in 308 and 115 blood samples from workers and controls, respectively.	**Exposure:** Workers were exposed to metallic antimony, antimony trioxide, and antimony pentasulfide. The antimony levels in the blood and urine were 0.5–20.2 and 0.5–18.2 mg/dL, respectively, in the workers in the dusty section of the facility and 0.5–18.2 mg/L and 0.5–16.2 mg/dL, respectively, in the less dusty section. The blood antimony level in the control group ranged from 0 to 3.3 mg/dL.	**Reproductive effects:** Reproductive disturbances were reported in 77.5% of the workers and 56% of controls. Increases in the occurrence of disturbances in the menstrual cycle were found (61.2% in workers and 35.7% in controls. Increases in spontaneous abortion (12.5%) were found in the workers, as compared to controls (4.1%). **Developmental effects:** Decreases in infant body weight gain were observed beginning at 6 months of age. By 12 months of age, infants of workers weighed 8.96 kg compared to 10.05 kg in the controls.
Brieger et al. 1954	112 workers involved in the production of grinding wheels. Workers were employed for 8 months to 2 years. No control group was used.	**Exposure:** Antimony trisulfide levels ranged from 0.42 to 3.9 mg Sb/m^3, with the majority of the findings >2.2 mg Sb/m^3. **Confounding exposure:** Workers were also exposed to phenol formaldehyde resin.	**Respiratory effects:** No signs of respiratory irritation were reported. **Cardiovascular effects:** Altered EKG readings (mostly T waves) were found in 37/75 workers. Increased blood pressure was observed in 14/112 workers and low blood pressure was observed in 24/112 workers; significance of these findings are not known since there was no control group. **Gastrointestinal effects:** A higher incidence of ulcers were found in the antimony exposed workers (63 per 1,000) compared to the total plant population (15 in 1,000).

Table 3-2. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Cooper et al. 1968	28 antimony process workers involved in extraction of antimony ore to antimony trioxide. Workers employed for 1–15 years. No control group was used.	**Exposure:** Antimony trioxide levels ranged from 0.081 to 138 mg Sb/m^3 at 47 locations within the facility.	**Respiratory effects:** No consistent alterations in lung function (only 14 subjects were examined). Pneumoconiosis was confirmed in three workers and suspected in five other workers.
Jones 1994	Retrospective cohort mortality study of 192 workers involved in the production of antimony metal, antimony alloys, and antimony trioxide. Employed for at least 3 months. Cause of death of maintenance workers and zircon plant worker, and office workers at the same facility was examined.	**Exposure:** No monitoring data were provided. **Confounding exposure:** Investigators noted that the workers were likely exposed to arsenic in the antimony ore. Smoking status was not included as a potential confounding variable.	**Respiratory effects:** No significant increases in deaths from respiratory effects. **Cancer:** Increase in lung cancer deaths in antimony workers and maintenance workers. Only significant in workers hired prior to 1940 and between 1946 and 1950. Workers with latency period of >20 years had the highest increase in lung cancer deaths.
Kim et al. 1999	Study of 12 workers (mean age of 35 years) exposed to antimony trioxide at a manufacturing facility for an average of 30 months. Another group of 22 workers (mean age of 33 years) at the facility not near the antimony sources was also examined. A second control group of 33 volunteers (mean age of 50 years) without occupational exposure to antimony was also examined.	**Exposure:** The mean antimony concentration in the exposed workers was 0.766 mg/m^3. Geometric mean urine antimony concentrations were 410.8, 112.5, and 27.8 µg/g creatinine in the exposed workers, control workers, and volunteer controls, respectively.	**Immunological effects:** Significant decreases in serum IgG1 and IgE levels were observed in exposed workers compared to control groups. A significant association between IgG4 levels and urine antimony levels were found in the exposed workers; no associations were found for other IgG subgroups or for IgE. No alterations in Il-2 or interferon-gamma levels were in the exposed workers, as compared to control workers.

Table 3-2. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Palacios et al. 2014	Linked data from the Nurses' Health Study with EPA's Air Toxic data (n=97,430 females).	**Exposure:** Median antimony concentrations for each exposure quartile were 0.000034, 0.000138, 0.000287, and 0.000682 µg/m^3.	**Neurological effects:** No significant association between antimony levels and risk of Parkinson's disease was found. Risk estimates were adjusted for age, smoking, and population density.
Potkonjak and Pavlovich 1983	51 males employed at a smelting facility. Mean duration of employment was 17.9 years (range of 9–31 years). All workers experienced pneumoconiotic changes. No control group was used.	**Exposure:** Workers were exposed to antimony oxides; 39–89% of dust was antimony trioxide and 2.1–7.8% was antimony pentoxide. No monitoring data were provided. **Confounding exposure:** Investigators noted that the airborne dust contained silica (0.82–4.72%), ferric trioxide (0.90–3.81%), and arsenic oxide (0.21–6.48%). No information on smoking was provided.	**Respiratory effects:** Clinical signs included chronic coughing (61%) and upper airway inflammation (35%). Respiratory effects included Type 1p pneumoconiosis (67%), chronic bronchitis (37%), chronic emphysema with pulmonary function changes (34%), inactive tuberculosis (18%), and pleural adhesions (28%). No consistent pattern of lung function alterations was found. **Dermal effects:** Dermatosis (63%) found predominantly in workers exposed to excessively high temperatures. **Ocular effects:** Conjunctivitis (28%).

Table 3-2. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
Renes 1953	78 males involved in smelting or employed as maintenance workers. Workers were employed for at least 2 weeks. No control group was used.	**Exposure:** Average concentrations in the breathing zone were 10.07 mg/m^3 in the furnace area and 11.81 mg/m^3 in the cupel area. **Confounding exposure:** Arsenic was present in smelting material; average levels of arsenic in the furnace and cupel areas were 1.10 and 0.36 mg/m^3, respectively. Workers were also exposed to hydrogen sulfide and iron oxide.	**Respiratory effects:** Soreness and bleeding of the nose (>70%), laryngitis (11%), and rhinitis (20%) of workers. **Gastrointestinal effects:** 11% reported gastrointestinal symptoms (abdominal cramps, diarrhea, vomiting). **Dermal effects:** Dermatitis (20%). **Neurological effects:** Nine workers reported nerve tenderness and tingling, severe headaches, and prostration. Antimony was detected in urine samples from 7/9 of these workers.
Schnorr et al. 1995	1,014 workers at an antimony smelter in Texas. Employed for at least 3 months; average length of employment was 6.8 years.	**Exposure:** Monitoring surveys conducted in 1975 and 1976 found geometric mean antimony levels of 0.5551 mg/m^3 using area samples and 0.747 mg/m^3 using personal samples. **Confounding exposure:** Investigators noted that the workers were also exposed to arsenic. Smoking status was not included as a potential confounding variable.	**Respiratory effects:** Increase in deaths from influenza (SMR=1.23) and pneumoconiosis/ other respiratory disease among workers with Spanish surnames. **Cardiovascular effects:** Increased deaths. from ischemic heart disease among Spanish surname workers as compared to a survey of Mexican-American population or to Spanish surnamed workers at a cadmium facility; the statistical significance of this finding was not reported. **Cancer:** Nonsignificant increase in deaths from lung cancer especially among workers with the longest period since first employed (>20 years) and the longest duration of employment (>10 years) (SMR=1.55; 90% CI 0.86–2.60). Significant positive trend in lung cancer deaths with increasing duration of employment when

Table 3-2. Health Effects in Humans Exposed to Antimony Dusts

Reference	Study population	Exposure	Outcomes
			compared to an ethnic-specific rate.
Stevenson 1965	Case series of 23 workers at an antimony smelter exposed to antimony trioxide dust and reporting dermatitis.	**Exposure:** Antimony concentrations were not reported; investigators noted that most of the antimony trioxide dust was <1 µm in diameter. **Confounding exposure:** The antimony sulfide ore contained minute traces of lead, arsenic, and iron; the investigators also noted that sulfur dioxide was released during the smelting process.	**Dermal:** Erythematous papules were most commonly reported in the antecubital area and shins. The investigators noted that these areas were most exposed to heat, which resulted in sweating. The rash typically subsided 3–14 days after the workers were transferred to cooler working environments.
Taylor 1966	Case series of seven workers acutely exposed to high levels of antimony trichloride.	**Exposure:** It is likely that the workers were exposed to up to 73 mg Sb/m^3. **Confounding exposure:** The workers were exposed to ≤146 mg/m^3 hydrogen chloride.	**Respiratory:** 7/7 workers reported upper respiratory tract soreness; this is likely due to the hydrogen chloride exposure. **Gastrointestinal:** Abdominal pain (4/7), vomiting (3/7), and anorexia (5/7) were reported by workers.

CI = confidence interval; EKG = electrocardiogram; EPA = Environmental Protection Agency; SMR = standardized mortality ratio

Respiratory Effects. Studies of workers exposed to antimony compounds (primarily antimony trioxide) have reported upper and lower respiratory effects. Upper respiratory effects included soreness and bleeding of the nose, rhinitis, and laryngitis in workers at an antimony smelter (Renes 1953). One of the more commonly reported lower respiratory effects is pneumoconiosis in workers involved in extraction of antimony trioxide from antimony ores and workers at antimony smelters (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Schnorr et al. 1995). Other lower respiratory effects include chronic coughing, upper airway inflammation, and chronic bronchitis (Potkonjak and Pavlovich 1983). In the two studies that conducted lung function tests, no consistent pattern of alterations was found (Cooper et al. 1968; Potkonjak and Pavlovich 1983). Three studies provided some monitoring data. In the study reporting upper respiratory effects, the average antimony concentrations were 10.07–11.81 mg/m^3 (Renes 1953). In the two studies reporting pneumoconiosis, antimony levels were 0.081–138 mg/m^3 in one study (Cooper et al. 1968) and 0.747 mg/m^3 (geometric mean concentration) in the second study (Schnorr et al. 1995). Several studies reported that the workers were also exposed to arsenic, which was present in the antimony ores (Jones 1994; Potkonjak and Pavlovich 1983; Renes 1953; Schnorr et al. 1995); the workers were also exposed to other compounds including iron oxide and hydrogen sulfide (Potkonjak and Pavlovich 1983; Renes 1953). In contrast to these studies of workers exposed to antimony ores and/or antimony oxides, respiratory irritation was not noted in workers exposed to ≤3.9 mg Sb/m^3 as antimony trisulfide for 8 months to 2 years (Brieger et al. 1954).

Studies in laboratory animals, particularly rats, support the findings of the epidemiology studies and suggest that the respiratory tract is one of the most sensitive targets of inhaled antimony toxicity. The lungs appear to be the most sensitive portion of the respiratory tract, and the severity of the respiratory effects appear to be concentration- and duration-related. Although most of the studies were conducted using antimony trioxide, studies with stibine (Price et al. 1979), antimony trisulfide (Brieger et al. 1954), and antimony ore (Groth et al. 1986) have also reported lung effects.

Exposure to antimony aerosols results in deposition of the particles in the lungs, which leads to increases in the number of alveolar macrophages, inflammation, and fibrosis. The earliest and most sensitive effect of inhaled antimony is increased alveolar and/or intra-alveolar macrophages. Intermediate- and chronic-duration studies found increases in alveolar and/or intra-alveolar macrophages in rats exposed to concentrations as low as 4.11 mg Sb/m^3 as antimony trioxide following a 13-week exposure (Newton et al. 1994) and 0.05 mg Sb/m^3 as antimony trioxide following a 1-year exposure (Newton et al. 1994). The increases in macrophages persisted for at least 27 weeks or 1 year, respectively, after exposure termination. The proliferation of macrophages is a normal physiological response to the deposition of

insoluble particulates in the lung and increases in the number of alveolar macrophages in the absence of evidence of lung damage were not considered adverse. The increases in antimony lung deposition also resulted in increases in lung clearance half-times. Following a 13-week exposure (Newton et al. 1994), the lung clearance half-times were 5.5 and 5.25 months in male and female rats, respectively, exposed to 4.11 mg Sb/m^3 and 10 and 8.25 months in male and female rats, respectively, exposed to 19.60 mg Sb/m^3; by comparison, the half-times were 3.75 months in both male and female rats exposed to 0.902 mg Sb/m^3. Similarly, in the 1-year exposure study (Newton et al. 1994; data reported in Bio/Dynamics 1990), the antimony lung clearance half-times in male and female rats were 3.0 and 4.2 months, respectively, at 0.43 mg Sb/m^3 and 8.7 and 10.2 months, respectively, at 3.8 mg Sb/m^3, as compared to 2.5 and 2.2 months, respectively, in the 0.05 mg Sb/m^3 group. The investigators noted that the decrease in lung clearance was higher than anticipated if it was solely due to volumetric overloading, suggesting that clearance was also affected by the intrinsic toxicity of antimony trioxide. In a 2-year study using smaller particles (mass median aerodynamic diameter [MMAD] of 1.0–1.4 μm compared to 3.05 μm in the Newton et al. [1994] study), estimated clearance half-times were 136, 206, and 262 days (approximately 4.5, 6.8, and 8.6 months) for exposures to 2.5, 8.3, and 25 mg Sb/m^3, respectively, as antimony trioxide (NTP 2016).

The lowest antimony trioxide concentrations resulting in histological alterations (lung inflammation) in rats are 19.60 and 0.43 mg Sb/m^3 in intermediate- and chronic-duration studies (Newton et al. 1994), respectively. In both studies, the increases in the incidence of lung inflammation were observed at the end of a 27-week or 1-year recovery period; these effects were not observed at the end of the exposure period (highest concentrations tested were 19.60 and 3.8 mg Sb/m^3 in the intermediate and chronic studies, respectively). In contrast, NTP (2016) found significant increases in the incidence in chronic inflammation and other lung lesions in rats exposed to ≥2.5 mg Sb/m^3 for 1 year; the smaller particle size in the NTP (2016) study may explain the difference between the studies. The lowest concentrations in mice resulting in lung inflammation are 25 mg Sb/m^3 following a 16-day exposure and 0.25 mg Sb/m^3 following a 2-year exposure (NTP 2016). Inflammation was also observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954) and in guinea pigs after intermediate-duration exposure to 37.9 mg Sb/m^3 as antimony trioxide (Dernehl et al. 1945). Chronic exposure to higher concentrations (≥1.6 mg Sb/m^3 as antimony trioxide or 17.5 mg Sb/m^3 as antimony ore) resulted in lung fibrosis (Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983). Other lesions observed in the lungs include proteinosis and alveolar/bronchiolar epithelial hyperplasia in rats and mice exposed to 2.5 mg Sb/m^3 as antimony trioxide for 1 or 2 years (NTP 2016), pulmonary edema and congestion in rats and guinea pigs exposed to a lethal stibine concentration of 1,395 mg Sb/m^3 for 30 minutes (Price et al.

1979), alveolar hypertrophy and hyperplasia and cholesterol clefts in rats exposed to 36 mg Sb/m^3 as antimony trioxide or 17.5 mg Sb/m^3 as antimony ore for 52 weeks (Groth et al. 1986) or rats exposed to 4.2 mg Sb/m^3 for 55 weeks (Watt 1983), lipoid pneumonia in rats exposed to 84–105 mg Sb/m^3 as antimony trioxide for 14.5 months (Gross et al. 1952), and focal hemorrhages in the lungs of rats exposed to 2.20 mg Sb/m^3 as antimony trisulfide for 6 weeks (Brieger et al. 1954).

The NTP (2016) 2-year antimony trioxide study also reported hyperplasia of the nasal respiratory epithelium in rats exposed to ≥2.5 mg Sb/m^3, squamous metaplasia of the respiratory epithelium in rats and mice exposed to 25 mg Sb/m^3, laryngeal epithelial hyperplasia in mice exposed to ≥8.3 mg Sb/m^3, and hyperplasia of tracheal epithelium in mice exposed to 25 mg Sb/m^3.

Cardiovascular Effects. Altered EKG readings were observed in workers exposed to 0.42–3.9 mg Sb/m^3 as antimony trisulfide for 8 months to 2 years (Brieger et al. 1954). Of the 75 workers examined, 37 showed changes in the EKG, mostly of the T-waves; these workers had also been exposed to phenol formaldehyde resin (Brieger et al. 1954). In a cohort mortality study, an increase in death from ischemic heart disease was observed among antimony smelter workers with Spanish surnames (Schnorr et al. 1995); the statistical significance of this finding was not reported. These limited data on cardiovascular effects in humans are supported by the finding of cardiac effects following parenteral administration of antimony to humans (see discussion of other routes of exposure in Section 3.2.4).

Inhalation exposure to antimony trisulfide dust (dust sample taken from an antimony production facility) resulted in degenerative changes in the myocardium and related EKG abnormalities (elevation of the RS-T segments and flattening of T-waves) in a variety of animal species (Brieger et al. 1954). Five days of exposure to 19.9 mg Sb/m^3 as antimony trisulfide resulted in EKG alterations in rabbits. In intermediate-duration studies, EKG alterations were observed in rats, rabbits, and dogs exposed to 2–4 mg Sb/m^3 as antimony trisulfide for 6–10 weeks (Brieger et al. 1954). It should be noted that elevated levels of arsenic were also present in the facilities' dust samples. This study also reported degenerative changes of the myocardium in rats, rabbits, and dogs exposed to antimony trisulfide, which consisted of hyperemia and swelling of myocardial fibers (Brieger et al. 1954). Most studies with antimony trioxide exposure did not find cardiovascular effects. No EKG alterations were observed in pigs exposed to 4.2 mg Sb/m^3 as antimony trioxide for 1 year (Watt 1983) or guinea pigs exposed to 37.9 mg Sb/m^3 for an intermediate-duration (Dernehl et al. 1945), and myocardial damage was not observed in rats exposed to concentrations as high as 19.60 mg Sb/m^3 for 13 weeks (Newton et al. 1994) or 36 mg Sb/m^3 for approximately 1 year (Groth et al. 1986; Newton et al. 1994; Watt 1980) or guinea pigs exposed to

37.9 mg Sb/m^3 for 2–30 weeks (Dernehl et al. 1945). NTP (2016) found chronic inflammation of the epicardium of mice exposed to ≥8.3 mg Sb/m^3 for 2 years and chronic inflammation of muscular arteries in rats exposed to ≥8.3 mg Sb/m^3.

Gastrointestinal Effects. A variety of gastrointestinal symptoms have been reported in workers engaged in activities including acute exposure to antimony trichloride (Taylor 1966) and chronic exposure to antimony trisulfide (Brieger et al. 1954) or antimony oxide (Renes 1953). The symptoms include abdominal pain, diarrhea, vomiting, and ulcers; no additional information was provided. A causal relationship to antimony exposure has not been definitely established because workers were exposed to a variety of other agents, in addition to antimony, that might cause or contribute to gastrointestinal effects (e.g., hydrogen chloride, sodium hydroxide) and the studies did not examine unexposed workers. Furthermore, in all likelihood, both inhalation and oral exposure to antimony occur at the workplace. Assuming that gastrointestinal effects are related to antimony exposure, site monitoring data indicate that effective exposure levels may range from approximately 2 to 70 mg Sb/m^3.

Symptoms of gastrointestinal disturbances were not reported in animals, and no histopathological alterations were observed in rats exposed to ≤36 mg Sb/m^3as antimony trioxide or 17.5 mg Sb/m^3 as antimony ore for 1 year (Groth et al. 1986; Watt 1980) or pigs exposed to 4.2 mg Sb/m^3 as antimony trioxide for 55 weeks (Watt 1983). However, chronic active inflammation was observed in the forestomach of mice exposed to 25 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016).

Hematological Effects. Information on the hematological toxicity of antimony is limited to a case report of three workers exposed to stibine, arsine, and hydrogen sulfide (Dernehl et al. 1944). Two of the three workers reported hematuria with weakness, headache, and abdominal and lumbar pain. It is not known if stibine was the causative agent of these effects. No studies were located regarding hematological effects in humans after inhalation exposure to other antimony compounds.

Toxicologically significant hematological effects have not been observed in rats and pigs following intermediate- or chronic-duration exposure to antimony aerosols ranging from approximately 4 to 20 mg Sb/m^3 as antimony trioxide (Newton et al. 1994; Watt 1983). One study reported decreases in total leukocyte counts and in polymorphonuclear leukocyte and eosinophil counts in guinea pigs exposed to 36.9 mg Sb/m^3 as antimony trioxide for 2–30 weeks (Dernehl et al. 1945) and another study reported hematopoietic cell proliferation in the spleen of female mice exposed to 25 mg Sb/m^3 for 2 years (NTP 2016).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to antimony.

No histopathological alterations were noted in the musculoskeletal system in rats exposed to 4.2 mg antimony/m^3 as antimony trioxide for 1 year (Watt 1980). Bone marrow hyperplasia was observed in rats exposed to 25 mg Sb/m^3 and mice exposed to ≥2.5 mg Sb/m^3 for 2 years (NTP 2016); the investigators noted that the hyperplasia in the mice was predominantly of myeloid cell type, which may have been secondary to the lung inflammation.

Hepatic Effects. No studies were located regarding hepatic effects in humans after inhalation exposure to antimony.

Parenchymatous or fatty degeneration was observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954) and in guinea pigs exposed to 37.9 mg Sb/m^3 as antimony trioxide for 2–30 weeks (Dernehl et al. 1945). No hepatic effects were observed in rats exposed to ≤36 mg Sb/m^3 as antimony trioxide for 1 year (Groth et al. 1986; Watt 1983) or 17.5 mg Sb/m^3 as antimony ore (Groth et al. 1986), or in rats or mice exposed to 25 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016).

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to antimony.

Two acute exposure studies have reported renal damage. Tubular dilation was observed in guinea pigs exposed to 799 mg Sb/m^3 as stibine gas for 30 minutes (Price et al. 1979) and parenchymatous degeneration was observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (Brieger et al. 1954). No renal effects were noted in rats exposed to 17.5 mg Sb/m^3 as antimony ore or up to 36 mg Sb/m^3 as antimony trioxide for 1 year (Groth et al. 1986; Watt 1983) or mice exposed to 25 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016). A 2-year exposure of rats resulted in an increase in hyaline droplet accumulation at ≥8.3 mg Sb/m^3 as antimony trioxide and nephropathy in female rats at 25 mg Sb/m^3 (NTP 2016).

Dermal Effects. Dermal effects have been reported in workers exposed to antimony oxides. These effects are likely due to direct skin contact with the antimony and are discussed in Dermal Effects portion of Section 3.2.3.2.

Ocular Effects. Ocular effects likely due to direct contact with stibine or antimony trioxide have been reported in animal studies. These findings are discussed in the Ocular Effects portion of Section 3.2.3.2.

NTP (2016) reported an increased incidence of ciliary body inflammation in rats exposed to 25 mg Sb/m^3 for 2 years. A non-concentration-related increase in retinal atrophy was also observed in female rats exposed to ≥2.5 mg Sb/m^3 (NTP 2016); the severity of the atrophy was similar to that observed in the concurrent controls. It is not known if these effects are due to direct contact or are systemic effects.

3.2.1.3 Immunological and Lymphoreticular Effects

One study examined the possible immunotoxicity of antimony in workers. In this study (Kim et al. 1999), decreases in IgG2 and IgE levels were found.

No animal studies evaluated immune function following inhalation exposure to antimony. In chronic-exposure studies, hyperplasia of the reticuloendothelial cells in the peribronchiolar lymph nodes was observed in female rats exposed to 3.8 mg Sb/m^3 as antimony trioxide for 1 year with a 1-year recovery period (Newton et al. 1994, incidence data reported in Bio/Dynamic 1990) and lymphoid hyperplasia was observed in the bronchial and mediastinal lymph nodes of rats and mice exposed to ≥2.5 mg Sb/m^3 as antimony trioxide for 2 years (NTP 2016). Another study reported the presence of mononuclear cell granulomas in rats exposed to17.5 mg Sb/m^3 as antimony ore for 1 year (Groth et al. 1986); this effect was not found in rats similarly exposed to 36 mg Sb/m^3 as antimony trioxide (Groth et al. 1986). The investigators noted that the granulomas were similar to those found in the early stages of silicosis and sarcoidosis.

3.2.1.4 Neurological Effects

A causal relationship between exposure to airborne antimony and neurological effects in humans has not been established. Nerve tenderness and a tingling sensation, headaches, and prostration were reported in workers exposed to antimony oxide at a concentration of 10.07 mg antimony/m^3 (Renes 1953). However, the factory workers were also exposed to arsenic, lead, copper, and possibly hydrogen sulfide and sodium hydroxide. Thus, it is difficult to determine if this effect was the result of antimony exposure. Another

study attempted to link air monitoring levels of antimony with the risk of Parkinson's disease in nurses and did not find a significant association (Palacios et al. 2014); it should be noted that the air concentrations were very low (the median level in the highest quartile was 0.000682 μg/m^3).

Information on the neurotoxicity of antimony in laboratory animals is limited to the chronic-duration studies that found no histological alterations in the brain of rats (Groth et al. 1986; NTP 2016; Watt 1983), mice (NTP 2016), or pigs (Watt 1983) exposed to antimony trioxide.

3.2.1.5 Reproductive Effects

Disturbances in the menstrual cycle were reported in 61.2% of women exposed to airborne metallic antimony, antimony pentasulfide, and antimony trioxide in a metallurgical plant compared to the 35.7% occurrence in controls (Belyaeva 1967); no other details were provided. No information (such as age and whether they had similar jobs as the workers) was provided that could be used to evaluate the appropriateness of the control group. The investigators noted that 77.5% of the workers and 56% of the controls had reproductive disturbances. The study also found an increase in the rate of spontaneous abortions (particularly late term abortions) in the workers (12.5%) as compared to the rate in controls (4.1%).

Data on the reproductive toxicity of antimony are limited to an intermediate-duration study conducted by Belyaeva (1967), which found a reduction in fertility (67% conceived compared to 100% in controls) in rats exposed to 209 mg Sb/m^3 as antimony trioxide. No histological alterations were observed in the reproductive tissues of rats exposed to antimony trioxide or antimony ore for 1 year (Groth et al. 1986; Watt 1983) or mice exposed to antimony trioxide for 2 years (NTP 2016). Increases in the incidence of epithelial hyperplasia were observed in the prostate of rats exposed to 2.5 or 8.3 mg Sb/m^3 for 2 years (NTP 2016).

The NOAEL and LOAEL values for reproductive effects in rats and mice are presented in Table 3-1 and Figure 3-1.

3.2.1.6 Developmental Effects

The study of women working at a metallurgical facility (Belyaeva 1967) also reported decreases in infant body weight gain beginning at 6 months of age; at 12 months of age, they weighed 11% less than infants from the control group. Interpretation of the results of this study is limited by the lack of information on

the control group, type of work the women performed, when the workers returned to work after giving birth, and information on confounding exposure to other compounds.

A decreased number of offspring was observed in rats exposed to 209 mg antimony/m^3 as antimony trioxide prior to conception and throughout gestation. No difference in fetal body weights was observed (Belyaeva 1967). This LOAEL for developmental effects in rats is presented in Table 3-1 and Figure 3-1.

3.2.1.7 Cancer

Several studies of antimony oxide workers have examined the carcinogenic potential of antimony. A significant positive trend in lung cancer deaths with increasing duration of employment was observed in workers at an antimony smelter facility (Schnorr et al. 1995). Similarly, another study of workers exposed to metallic antimony, antimony alloys, and antimony trioxide found increases in lung cancer deaths in workers hired prior to 1940 or between 1946 and 1950 (Jones 1994). In both studies, the workers were also exposed to arsenic and neither study included smoking status as a confounding variable.

Four studies have evaluated the carcinogenicity of antimony trioxide in rats. Increases in lung neoplasms (squamous cell carcinomas, bronchioalveolar adenomas and carcinomas, and scirrhous carcinoma) were observed in female rats exposed to 4.2 mg Sb/m^3 for 55 weeks with a 1-year recovery period (Watt 1983) or 36 mg Sb/m^3 for 52 weeks with a 20-week recovery period (Groth et al. 1986). However, a third study (Newton et al. 1994) did not find any neoplasms in male or female rats exposed to 3.8 mg Sb/m^3 for 1 year with a 1-year recovery period. Newton et al. (1994) stated that a pathologist who examined the slides from the Groth et al. (1986), Watt (1983), and Newton et al. (1994) studies noted more extensive lung damage and a considerable higher amount of antimony trioxide in the lungs of rats tested in the Watt (1983) study as compared to those tested in the Newton et al. (1994) study even though the concentrations were similar, suggesting that the actual concentrations tested by Watt (1983) may have been higher than reported. A fourth study found significant increases in the incidence of alveolar/bronchiolar adenomas at 8.3 mg Sb/m^3 and benign pheochromocytomas in the adrenal gland of rats exposed to 25 mg Sb/m^3 for 2 years (NTP 2016). Increases in lung neoplasms were also observed in rats exposed to 17.5 mg Sb/m^3 as antimony ore for 52 weeks followed by a 1-year recovery period (Groth et al. 1986). In mice, a 2-year exposure to antimony trioxide resulted in significant increases in alveolar/bronchiolar adenomas, carcinomas, or combined incidences at ≥2.5 mg Sb/m^3, malignant lymphomas in females exposed to ≥2.5 mg Sb/m^3, and fibrous histiocytomas in the skin of males exposed to 25 mg Sb/m^3 (NTP 2016). No

increases in lung tumors were observed in pigs exposed to 4.2 mg Sb/m^3 as antimony trioxide (Watt 1983).

The CELs are recorded in Table 3-1 and Figure 3-1.

3.2.2 Oral Exposure

Health effects have been observed in humans and animals following oral exposure to a variety of antimony compounds. Adverse effects following exposure to antimony potassium tartrate (an organic form of trivalent antimony), antimony trichloride, antimony trioxide, and metallic antimony are discussed below. It should be noted that the results of the NTP (1992) study were published by Dieter et al. (1991); these data will only be cited to NTP (1992) to avoid confusion that these are separate studies.

3.2.2.1 Death

No studies were located regarding death in humans after oral exposure to antimony.

Mortality was not observed in rats following a single exposure to ≤188–17,000 mg Sb/kg as antimony trioxide (Fleming 1982; Myers et al. 1978; Smyth and Carpenter 1948; Smyth and Thompson 1945) or to a 7,000 mg Sb/kg dose of metallic antimony (Bradley and Frederick 1941). However, a lower single dose of organic antimony (300 mg Sb/kg dose as antimony potassium tartrate) resulted in death in rats (Bradley and Frederick 1941). Death was attributed to myocardial failure. Significant increases in deaths were not observed in rats or mice exposed to 61 or 150 mg Sb/kg/day as antimony potassium tartrate in drinking water for 14 days (NTP 1992). These data for death in animals suggest that organic antimony is more lethal than the inorganic compounds, probably due to increased absorption of the antimony potassium tartrate, likely due to its increased solubility.

Intermediate-duration exposure to inorganic antimony compounds or metallic antimony did not result in increases in deaths in rats exposed to ≤1,570 mg Sb/kg/day as antimony trioxide in the diet (Hext et al. 1999; Hiraoka 1986) or ≤850 mg Sb/kg/day as metallic antimony (Hiraoka 1986). Chronic administration of a low dose of antimony potassium tartrate (0.63 mg Sb/kg/day) resulted in decreased lifespan in rats (Schroeder et al. 1970). A decrease in survival was also noted in female mice exposed to 0.35 mg Sb/kg/day as antimony potassium tartrate (Kanisawa and Schroeder 1969); however, there was no statistical analysis of the data.

The reliable LOAEL values are presented in Table 3-3 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAELs for each systemic effect in each laboratory species and duration are presented in Table 3-3 and plotted in Figure 3-2; summaries of epidemiology studies are presented in Table 3-4.

Respiratory Effects. In the only human study examining respiratory end points, no significant association between urinary antimony levels and the prevalence of asthma was found among participants in the 2007–2008 National Health and Nutrition Examination Survey (NHANES) (Mendy et al. 2012).

No histological alterations were observed in the respiratory tract in several studies at the highest doses tested; the highest NOAEL values were 61 or 150 mg Sb/kg/day in rats or mice, respectively, exposed to antimony potassium tartrate in drinking water for 14 days (NTP 1992), 1,408 mg Sb/kg/day in rats exposed to antimony trioxide in the diet for 90 days (Hext et al. 1999), and 42.17 mg Sb/kg/day in rats exposed to antimony potassium tartrate in drinking water for 13 weeks (Poon et al. 1998).

Cardiovascular Effects. Several investigators have utilized the NHANES dataset to examine the possible association between antimony and cardiovascular toxicity. No significant associations were found between urinary antimony levels and the prevalence of congestive heart failure, coronary heart disease, angina pectoris, heart attack, or stroke (Mendy et al. 2012). In two studies, significant associations between urinary antimony levels and the prevalence of high blood pressure were found in adults (Shiue and Hristova 2014; Shiue 2014); antimony accounted for 6.2% of the population risk (Shiue and Hristova 2014).

No histopathological alterations were observed in the heart following acute-duration exposure of rats and mice to 61 or 150 mg Sb/kg/day as antimony potassium tartrate (NTP 1992) or following intermediate-duration exposure to 1,408 mg Sb/kg/day as antimony trioxide (Hext et al. 1999) or 42.17 mg Sb/kg/day as antimony potassium tartrate (Poon et al. 1998). In studies evaluating cardiovascular function, no significant alterations in blood pressure were observed in rats exposed to 0.7 mg Sb/kg/day as antimony trichloride during pregnancy and/or lactation (Angrisani et al. 1988; Marmo et al. 1987; Rossi et al. 1987) or rats chronically exposed to 0.63 mg Sb/kg/day as antimony potassium tartrate (Schroeder et al. 1970).

Table 3-3. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Results	Reference/comments
ACUTE EXPOSURE									
Systemic									
1	Rat (F344/N) 10M, 10F	14 days (W); 0, 5.8, 10, 21, 34, and 61 mg Sb/kg/day	BW, WI, CS, OW, HP	Resp Cardio Gastro Musc/Skel Hepatic Renal Endocr Bd wt	61 61 61 61 61 61 61 61			No histological or body weight alterations were observed.	NTP 1992; Dieter et al. 1991 (antimony potassium tartrate)
2	Mouse (B6C3F1) 10M, 10F	14 days (W); 0, 21, 36, 63, 99, and 150 mg Sb/kg/day	BW, WI, CS, OW, HP	Resp Cardio Gastro Musc/Skel Hepatic Renal Endocr Bd wt	150 150 99[b] 150 99 150 150 63	 150 150 99		Focal ulceration in the forestomach in 4/10 mice and minimal-to-moderate hepatocellular cytoplasmic vacuolization in 10/10 mice. Decreased body weight gain was observed at 63 and 99 mg Sb/kg/day in males and females, respectively; midway through the study. Final body weights were within 93% of the controls. Dramatic decreases in water consumption were observed at all doses.	NTP 1992; Dieter et al. 1991 (antimony potassium tartrate)
3	Dog (Beagle) 13 M,F	Once (W); 4.8 mg Sb/kg	CS	Gastro		4.8		The mean latency to vomit was 30 minutes.	Houpt et al. 1984 (antimony potassium tartrate)
INTERMEDIATE EXPOSURE									
Systemic									
4	Rat (NS) 30F	22 days (W); 0, 0.07, and 0.8 mg Sb/kg/day	BW, OF	Cardio Bd Wt	0.8 0.8			No significant alterations in body weight or blood pressure were found in the dams.	Angrisani et al. 1988; Marmo et al. 1987 (antimony trichloride)
5	Rat 10NS	14-20 days (GW); 0, 390-500 mg Sb/kg	CS, BW, GN	Gastro Bd wt	500 500			No evidence of digestive upset or alterations in body weight.	Fleming 1938 (antimony trioxide)
6	Rat (NS) 10M	Daily 130 days (F); 0 or 1500 mg Sb/kg	BW, FI, GN, HP	Bd Wt		1500		Terminal body weight reduced 16% relative to pair-fed controls.	Gross et al. 1955 (antimony trioxide)

Table 3-3. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Results	Reference/comments
7	Rat (Wistar) 12M, 12F	Daily 90 days (F); M: 0, 70, 353, and 1408 mg Sb/kg/day; F: 0, 81, 413, and 1570 mg Sb/kg/day	CS, OP, BW, FI, UR, HE, BC, OW, HP	Resp Cardio Gastro Hemato Muscu/skel Hepatic Renal Endocr Ocular Bd Wt	1408 1408 1408 1408 1408 1408 1408 1408 1408 1408			No alterations in hematological or serum chemistry indices or histopathology were observed.	Hext et al. 1999 (antimony trioxide)
8	Rat (Wistar) 12M	12 weeks (F); 0 or 700 mg Sb/kg/day	CS, BW, OW, HE, BI	Hemato Bd Wt	700 700			No alterations in hematological parameters or body weight gain.	Hiraoka 1986 (antimony trioxide)
9	Rat (Wistar) 12M	12 weeks (F); 0, 85, or 850 mg Sb/kg/day	CS, BW, OW, HE, BI	Hemato Bd Wt	850	85		Body weight was decreased 10% at 85 mg Sb/kg/day and 18% at 850 mg Sb/kg/day. Food consumption data were not provided.	Hiraoka 1986 (antimony metal)
10	Rat (Sprague Dawley) 15M, 15F	Daily 13 weeks (W); M: 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day; F: 0, 0.06, 0.64, 6.13, and 45.69 mg Sb/kg/day	BW, FI, WI, HE, BI, OW, HP	Resp Cardio Gastro Hemato Hepatic Renal Endocr Dermal Bd Wt Metab Other (spleen)	42.17 42.17 42.17 5.58 42.17 42.17 42.17 42.17 42.17 0.06[c] 0.06	 42.17 0.64 0.64		**Hematological:** A 5% decrease in red blood cell levels and 12% decrease in platelet counts were observed in male rats exposed to 42.17 mg Sb/kg/day. **Hepatic:** Liver effects included minimal nuclear anisokaryosis in males at ≤5.58 mg Sb/kg/day and females at 0.06 mg Sb/kg/day and mild nuclear anisokaryosis at higher doses. These alterations were considered adaptive and not biologically significant. **Endocrine:** Minimal to mild epithelial changes (increased cell height, decreased follicle size, and nuclear vesiculations) were observed in the thyroid at ≥0.06 mg Sb/kg/day. **Metabolic:** Decreases in serum glucose levels (15-17%) were observed in females exposed to ≥0.64 mg Sb/kg/day. **Other:** In the spleen, mild sinus congestion was observed at ≥0.56 mg Sb/kg/day in males and hyperplasia was observed at ≥0.64 mg Sb/kg/day in females and at 42.17 mg Sb/kg/day in males.	Poon et al. 1998 (antimony potassium tartrate)

Table 3-3. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Results	Reference/comments
11	Rat (NS) 10F	44 days; 0, 0.07, 0.7 mg Sb/kg/day	BW, OF	Cardio Bd Wt	0.7 0.07	0.7		No alterations in blood pressure; 11% decrease in body weight gain.	Rossi et al. 1987; Marmo et al. 1987 (antimony trichloride)
12	Rat (NS) 10M	Daily 30 days (F); 0, 50, 230, 890 mg Sb/kg/day	BW, OW, HE	Hemato Renal Bd Wt	230 890 230	894 890		Significantly increased (21%) red blood cell count. Decreased body weight gain accompanied with a decrease in food consumption.	Smyth and Thompson 1945 (antimony trioxide)
13	Rat (Wistar) 5M	Daily 24 weeks (F); 0, 370, 740, 1,500 mg Sb/kg/day	CS, BW, FI, WI, OW, HE, BI, HP	Hemato Hepatic Bd Wt	740 370 740	1500 740 1500		Reduced terminal body weight, hematocrit, hemoglobin, and serum albumin/globulin ratio; increased total serum protein. Increased incidence of disorder of the hepatic cords at 740 and 1500 mg Sb/kg/day and cloudy swelling in the hepatic cords at 1500 mg Sb/kg/day.	Sunagawa 1981 (antimony metal)
14	Rat (Wistar) 5M	Daily 24 weeks (F); 0, 620, 1,200 mg Sb/kg/day	CS, BW, FI, WI, OW, HE, BI, HP	Hemato Hepatic Bd Wt	 1200	620 620		Reduced red blood cell count (22%) at 620 and 1200 mg Sb/kg/day; increased incidence of cloudy swelling in hepatic cords at 620 (3/5) and 1200 (2/5) mg Sb/kg/day, as compared to controls (0/5).	Sunagawa 1981 (antimony trioxide)
Immunological and Lymphoreticular Effects									
15	Rat (Sprague Dawley) 15M, 15F	Daily 13 weeks (W); M: 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day; F: 0, 0.06, 0.64, 6.13, and 45.69 mg Sb/kg/day	BW, FI, WI, HE, BI, OW, HP	 0.06		0.56		An increase in medullary volume in thymus gland in males at ≥0.56 mg Sb/kg/day and females at ≥6.13 mg Sb/kg/day; the study did not evaluate immune function.	Poon et al. 1998 (antimony potassium tartrate)
Reproductive Effects									
16	Rat (Crj:Wistar) 7-8M	3 days/week 4 weeks (G); 0, 10, or 1000 mg Sb/kg	OW, HP		1000			No significant alterations in sperm count, motility, or morphology or histological alterations in testes were observed.	Omura et al. 2002 (antimony trioxide)
17	Rat (Crj:Wistar) 8M	3 days/week 4 weeks (G); 0 or 10 mg Sb/kg	OW, HP		10			No significant alterations in sperm count, motility, or morphology or histological alterations in testes were observed.	Omura et al. 2002 (antimony potassium tartrate)

Table 3-3. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Results	Reference/comments
18	Mouse (Crj:CD) 9-10M	5 days/week 4 weeks (G); 0, 10, or 1000 mg Sb/kg	OW, HP		1000			No significant alterations in sperm count or morphology or histological alterations in testes were observed.	Omura et al. 2002 (antimony trioxide)
19	Mouse (Crj:CD) 10M	5 days/week 4 weeks (G); 0 or 10 mg Sb/kg	OW, HP		10			No significant alterations in sperm count or morphology or histological alterations in testes were observed.	Omura et al. 2002 (antimony potassium tartrate)
Developmental Effects									
20	Rat (NS) 30F	44 days; 0, 0.07, 0.7 mg Sb/kg/day	BW, OF		0.07	0.7		Decreased pup growth on PND10-60; pups weighed 26% and 47% less than controls on PND 10 and 22, respectively.	Rossi et al. 1987 (antimony trichloride)
21	Rat (NS) 10M,F	38 days; 0, 0.1, 1 mg Sb/kg/day	BW, OF			0.1		Significant alterations in vasomotor response to 1-noradrenaline and 1-isoprenaline at ≥0.1 mg Sb/kg/day at 60 days of age and to acetylcholine at 1 mg Sb/kg/day at 60 days of age.	Rossi et al. 1987; Marmo et al. 1987 (antimony trichloride)
22	Rat (NS) 10M,F	38 days (W); 0, 0.1, 1 mg Sb/kg/day	BW; OF			0.1		Altered vasomotor response to 1-noreadrenaline and 1-isoprenaline in pups at 0.1 mg Sb/kg/day and to acetylcholine at 1 mg Sb/kg/day, no alterations in systolic blood pressure or body weight.	Angrisani et al. 1988; Marmo et al. 1987 (antimony trichloride)
CHRONIC EXPOSURE									
Death									
23	Mouse (CD-1); 54M, 54F	Lifetime; (W); 0 or 0.35 mg Sb/kg/day	LE, BW, HP				0.35	Decreased survival in females.	Kanisawa and Schroeder 1969 (antimony potassium tartrate)
24	Rat (Long-Evans) 50-60M, 50-60F	Lifetime (W); 0 or 0.63 mg Sb/kg/day	LE, BW, OW, UR, GN				0.63	Exposure to antimony significantly reduced survival rate in male and female rats. At the median life spans, males survived 106 days and females 107 days less than controls.	Schroeder et al. 1970 (antimony potassium tartrate)

Table 3-3. Levels of Significant Exposure to Antimony – Oral

Figure key[a]	Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Results	Reference/comments
Systemic Effects									
25	Rat (Long-Evans) 50-60M, 50-60F	Lifetime (W); 0 or 0.63 mg Sb/kg/day	LE, BW, OW, UR, GN	Cardio Bd Wt Metab	0.63 0.63	 0.63		Decreased (28-30%) non-fasting serum glucose in males and females.	Schroeder et al. 1970 (antimony potassium tartrate)
26	Mouse (CD-1) 54 M, 54F	Lifetime; 0 or 0.35 mg Sb/kg/day	LE, BW, HP	Hepatic Bd Wt	0.35 0.35			No histological alterations in the liver or alterations in body weight gain.	Kanisawa and Schroeder 1969 (antimony potassium tartrate)

[a]The number corresponds to entries in Figure 3-2.
[b]Used to derive an acute-duration oral MRL of 1 mg Sb/kg/day based on a NOAEL of 99 mg Sb/kg/day and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive an intermediate-duration oral MRL of 0.0006 mg Sb/kg/day based on a NOAEL of 0.06 mg Sb/kg/day and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Parameters monitored: BC = biochemistry; BI = biochemical changes; BW = body weight; CS = clinical signs; FI = food intake; GN = gross necropsy; HE = hematology; HP = histopathology; LE = lethality; OP = ophthalmology; OF = organ function; OW = organ weight; UR = urinalysis; WI = water intake;

Cardio = cardiovascular; CI = confidence interval; d = day(s); Endocr = endocrine; F = female(s); Gastro = gastrointestinal; GC = gas chromatography; Hemato = hematological; hr = hour(s); M = male(s); MRL = Minimal Risk Level; NS = not specified; Resp = respiratory; Sb = antimony

Figure 3-2. Levels of Significant Exposure to Antimony - Oral

Acute (≤ 14 days)

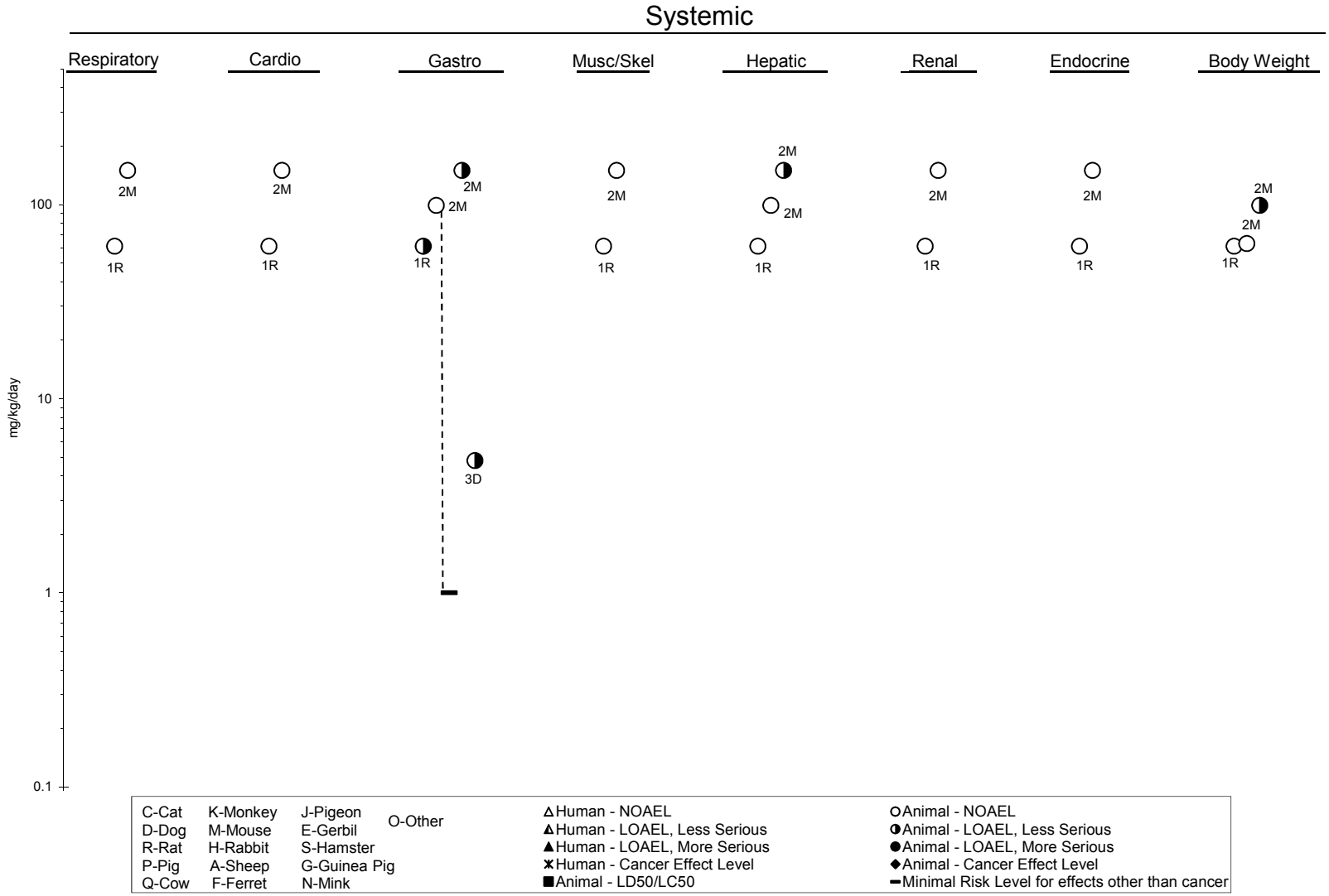


Figure 3-2. Levels of Significant Exposure to Antimony - Oral *(Continued)*

Intermediate (15-364 days)

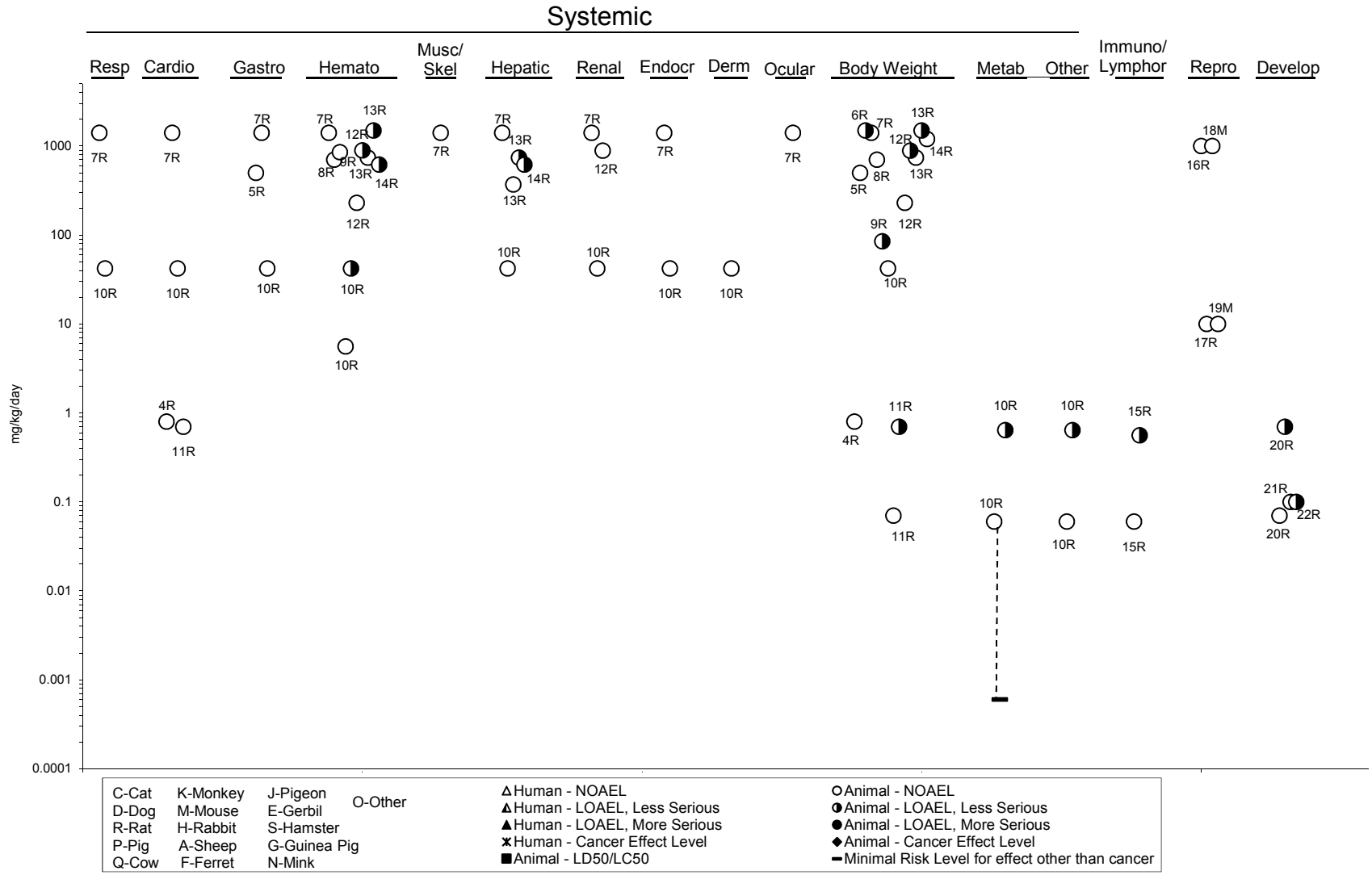


Figure 3-2. Levels of Significant Exposure to Antimony - Oral *(Continued)*

Chronic (≥365 days)

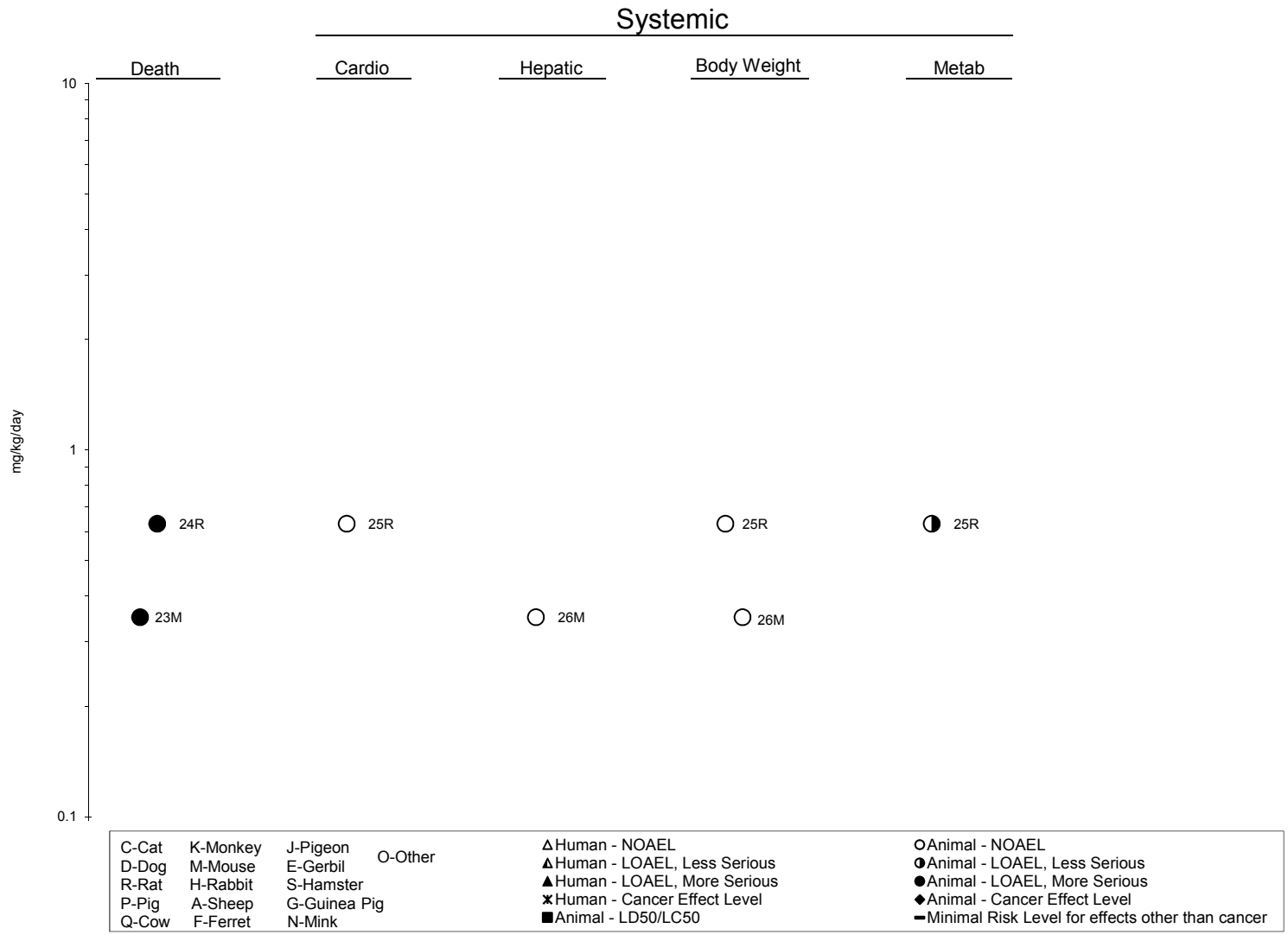


Table 3-4. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Colak et al. 2015	Populations living in two cities in Turkey near the Black Sea; 13,012 cancer cases were registered in 2000–2007.	541 water samples were collected from the area; antimony levels were <20 µg/L in all samples.	**Cancer effects:** A positive relationship between antimony levels and cancer incidence was found. The study examined 17 metals and found that, in total, they accounted for only 8.2% of the cancer incidence of the population.
Longerich et al. 1991	Case-control study of 28 women in Newfoundland, Canada with an infant diagnosed with neural tube defect; mothers of age-matched infants living in the same geographical region served as controls.	Mean antimony levels in drinking water were 0.02 and 0.11 ppb in the control and case groups, respectively.	**Developmental effects:** No significant difference in antimony drinking water levels between the cases and controls.
Mendy et al. 2012	1,857 adults (49.6% males, 50.4% females; mean age of 50.3 years) participating in the 2007–2008 NHANES.	Geometric mean urinary antimony level was 0.06 µg/g creatinine (95% CI 0.06–0.06).	Medical conditions were self-reported. **Respiratory effects:** No significant association with asthma. **Cardiovascular effects:** No significant associations for congestive heart failure, coronary heart disease, angina pectoris, heart attack, or stroke. **Hepatic effects:** No significant associations with liver conditions. **Endocrine effects:** No significant association with thyroid conditions. **Other systemic effects:** No significant association with gout. **Cancer effects:** No associations with cancer.

Table 3-4. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Shiue 2014	5,864 adults aged ≥20 years participating in 2011–2012 NHANES. High blood pressure (systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg) was found in 31.1% of the total population (this rate includes children, which were not included in the statistical analyses); blood pressure classification was based on a single blood pressure measurement.	Urinary antimony level (mean levels were not reported in the study) was the biometric used for the analyses; urine samples were collected by 20–30% of the whole NHANES cohort.	**Cardiovascular effects:** Significant association between urinary antimony levels and high blood pressure; OR of 1.56 (95% CI 1.29–1.89) with adjusting for urine creatinine levels, age, sex, body mass index, and ratio of family income to poverty level. In weighted model (also includes adjustment for subsample weighting), the OR was 1.39 (95% CI 1.10–1.77). The study also found significant associations for several other metals (cobalt, cesium, manganese, lead, tin, platinum, molybdenum, thallium, and tungsten).
Shiue 2015	5,031 adults (48.4% males, 51.6% females) aged 20-–9 years participating in 2009–2010 NHANES; the mean age was 44 years. Ankylosing spondylitis assessed via clinical measures of occiput-to-wall distance and chest expansion; values of >2 and >2.5 cm were considered abnormal; active lumbar flexion was also used to assess ankylosing spondylitis but the criterion was not reported.	Urinary antimony level (mean levels were not reported in the study) was the biometric used for the analyses; urine samples were collected by 20–30% of the whole NHANES cohort.	**Musculoskeletal effects:** Significant association between urinary antimony levels and occiput-to-wall distance; OR of 1.74 (95% CI 1.15–2.62). No association with chest expansion (OR 0.90; 95% CI 1.65–1.29) or active lumbar flexion (OR -0.05; 95% CI -0.17–0.03).
Shiue and Hristova 2014	Adults aged ≥20 years participating in 2009–2012 NHANES; based on data presented in the paper, 2,391 participants were ≥18 years for age. See Shiue (2014) for blood pressure criteria.	Urinary antimony level (mean levels were not reported in the study) was the biometric used for the analyses; urine samples were collected by 20–30% of the whole NHANES cohort.	**Cardiovascular effects:** Significant association between urinary antimony levels and high blood pressure; OR of 1.99 (95% CI 1.30–1.95) with adjusting for urine creatinine levels, age, sex, body mass index, and ratio of family income to poverty level. In weighted model (also includes adjustment for subsample weighting), the OR was 1.44 (95% CI 1.12–1.86). The investigators estimated that antimony accounted for 6.2% of the population risk.

Table 3-4. Health Effects in Humans Orally Exposed to Antimony

Reference	Study population	Exposure	Outcomes
Zheng et al. 2014	1,106 women in China.	Umbilical cord antimony was measured.	**Developmental effects:** Median umbilical cord antimony was significantly higher in women with adverse pregnancy outcomes (18.6 µg/L) compared to controls (0.16 µg/L); however, the risk of adverse pregnancy outcome in association with antimony was not statistically significant.

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio

Alterations in vasomotor responses were observed in pups exposed to antimony chloride; these effects are discussed under Developmental Effects.

Gastrointestinal Effects. Shortly after drinking lemonade contaminated with antimony potassium, workers began to vomit (Dunn 1928). Gastrointestinal effects have also been reported in factory workers after exposure to airborne antimony dust. As discussed in Section 3.2.1.2, the gastrointestinal effects probably resulted from swallowing the antimony dust.

Vomiting was observed in dogs following a single exposure to antimony potassium tartrate (Houpt et al. 1984). Other studies have not reported overt signs of gastrointestinal effects in rats or mice following acute- or intermediate-duration exposures to antimony trioxide or antimony potassium tartrate (Fleming 1982; Hext et al. 1999; NTP 1992; Poon et al. 1998). Focal ulceration was observed in the forestomach of mice exposed to 150 mg Sb/kg/day as antimony potassium tartrate for 2 weeks (NTP 1992). Histological alterations were not observed in rats (Hext et al. 1999; NTP 1992; Poon et al. 1998).

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to antimony.

Animal studies have examined potential hematological effects of three antimony compounds (metallic antimony, antimony trioxide, and antimony potassium tartrate) following intermediate-duration exposure. No alterations in hemoglobin levels or hematocrit were observed in rats exposed to 850 mg Sb/kg/day as metallic antimony; however, a decrease in hematocrit level was observed 4 weeks postexposure (Hiraoka 1986). In a second study, no consistent dose-related alterations in red blood cell counts were observed in rats exposed to 370–1,500 mg Sb/kg/day; however, significant decreases in hemoglobin and hematocrit were observed at 1,500 mg Sb/kg/day (Sunagawa 1981). Mixed results were found for antimony trioxide. Smyth and Thompson (1945) reported an increase in red blood cell count in rats at 894 mg Sb/kg/day and Sunagawa (1981) reported a decrease in red blood cell counts at 620 mg Sb/kg/day; neither study found alterations in hemoglobin levels. In contrast, no alterations in hematological parameters (including red blood cell counts) were found in rats exposed to 700 mg Sb/kg/day (Hiraoka 1986) or 1,408 mg Sb/kg/day (Hext et al. 1999). Decreases in red blood cell and platelet counts were observed in male rats exposed to 42.17 mg Sb/kg/day as antimony potassium tartrate; no effects were found in female rats (Poon et al. 1998). The inconsistent findings across studies and compounds preclude determining whether antimony adversely affects the hematological system.

Musculoskeletal Effects. Shiue (2015) found a significant association between urinary antimony levels and one of the three clinical measures of ankylosing spondylitis among adults participating in the NHANES; however, no associations were found for the other two measures of ankylosing spondylitis.

No histological alterations in musculoskeletal tissue were observed in rats or mice acutely exposed to 61 or 150 mg Sb/kg/day as antimony potassium tartrate (NTP 1992) or in rats exposed to 1,408 mg Sb/kg/day as antimony trioxide for 90 days (Hext et al. 1999).

Hepatic Effects. Mendy et al. (2012) did not find a significant association between urinary antimony levels and liver conditions among NHANES participants.

Minimal to mild hepatocellular cytoplasmic vacuolization, primarily in the centrilobular region, was observed in mice exposed to 150 mg Sb/kg/day as antimony potassium tartrate for 2 weeks (NTP 1992). Minimal cloudy swelling of the hepatic cords has been observed in rats exposed to 620 mg Sb/kg/day as antimony trioxide or 740 mg Sb/kg/day as metallic antimony for 24 weeks (Sunagawa 1981). Increases in the incidence of nuclear anisokaryosis and hepatocellular portal density were observed in all groups of rats exposed to antimony potassium tartrate in the drinking water for 13 weeks (Poon et al. 1998); the severity of either alteration was considered mild in males at ≥5.58 mg Sb/kg/day and in females at ≥0.64 mg Sb/kg/day. However, these alterations are adaptative changes and were not considered to be biologically adverse. Other studies have not found hepatic effects at doses as high as 61 mg Sb/kg/day as antimony potassium tartrate in rats for 14 days (NTP 1992), 1,408 mg Sb/kg/day as antimony trioxide in rats for 90 days (Hext et al. 1999), or 0.35 mg Sb/kg/day as antimony potassium tartrate in mice for lifetime exposure (Kanisawa and Schroeder 1969).

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to antimony.

Animal studies have not reported histological alterations in the kidneys of rats and mice acutely exposed to 61 or 150 mg Sb/kg/day as antimony potassium tartrate (NTP 1992), rats exposed to ≤1,408 mg Sb/kg/day as antimony trioxide for an intermediate duration (Hext et al. 1999; Smyth and Thompson 1945), or rats exposed to 42.17 mg Sb/kg/day as antimony potassium tartrate for an intermediate duration (Poon et al. 1998).

Endocrine Effects. No significant association between urinary antimony levels and self-reported thyroid conditions were found in NHANES participants (Mendy et al. 2012).

In general, studies examining endocrine organs have not reported adverse effects at 61 or 150 mg Sb/kg/day as antimony potassium tartrate in rats and mice exposed for 14 days (NTP 1992) or in rats exposed to 1,408 mg Sb/kg/day as antimony trioxide for 90 days (Hext et al. 1999). Poon et al. (1998) reported minimal to mild epithelial changes in the thyroid of rats exposed to ≥0.06 mg Sb/kg/day; however, the alterations were not dose-related and did not appear to affect thyroid function, and the investigators did not consider them adverse.

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to antimony. No dermal effects were observed in rats exposed to antimony trioxide in drinking water for 13 weeks at doses as high as 42.17 mg Sb/kg/day (Poon et al. 1998).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to antimony. No histological alterations were observed in the eyes of rats exposed to 1,408 mg Sb/kg/day as antimony trioxide for 90 days (Hext et al. 1999).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to antimony.

Most studies have not reported decreases in body weight gain in laboratory animals exposed to metallic antimony, antimony trioxide, or antimony potassium tartrate (Angrisani et al. 1988; Fleming 1982; Hext et al. 1999; Hiraoka 1986; Kanisawa and Schroeder 1969; NTP 1992; Poon et al. 1998; Schroeder et al. 1970; Sunagawa 1981); the highest NOAEL values identified in these studies are listed in Table 3-3. Four studies did report decreases in body weight and/or weight loss. NTP (1992) reported significant decreases in body weight gain in mice exposed to 99 mg Sb/kg/day (males) or 150 mg Sb/kg/day (males and females). Although these decreases in body weight gain were observed midway through the 2-week study, the body weights of all groups of mice were within 93% of the controls at termination. Decreases in body weight gain (body weights were 11–18% lower than controls) were observed in rats exposed to ≥85 mg Sb/kg/day as metallic antimony for 12 weeks; the lower body weights in the 850 mg Sb/kg/day group were still lower than controls after a 12-week recovery period (Hiraoka 1986). Smyth and Thompson (1945) reported a decrease in body weight gain in rats exposed to 890 mg Sb/kg/day as antimony trioxide in the diet for 30 days; however, a decrease in food intake was also observed at that

dose level. A fourth study reported an 11% decrease in maternal weight gain in rats exposed to 0.7 mg Sb/kg/day as antimony trichloride in drinking water during gestation and lactation (Rossi et al. 1987).

Metabolic Effects. No studies were located regarding metabolic effects in humans after oral exposure to antimony.

Two studies have reported significant decreases in serum glucose levels following exposure to antimony potassium tartrate. In an intermediate-duration study, dose-related decreases in serum glucose levels were observed in female rats at ≥0.64 mg Sb/kg/day (Poon et al. 1998); the investigators did not report whether blood samples were from fasting or nonfasting rats. ATSDR notes that the serum glucose levels in all groups (including controls) were higher than the normal range reported by the animal supplier (Charles River Laboratories 2006). Decreases in nonfasting glucose were observed in male and female rats exposed for a lifetime to 0.63 mg Sb/kg/day as antimony potassium tartrate (Schroeder et al. 1970); no significant alterations in fasting glucose levels were found.

Other Systemic Effects. Mendy et al. (2012) did not find a significant association between urinary antimony levels and the incidence of self-reported gout among NHANES participants.

Splenic sinus congestion in males at ≥0.56 mg Sb/kg/day, sinus hyperplasia in females at ≥0.64 Sb/kg/day and males at 42.17 Sb/kg/day, and arterial cuff atrophy in males at 42.17 mg Sb/kg/day were observed in rats exposed to antimony potassium tartrate (Poon et al. 1998).

Two studies reported alterations in serum cholesterol levels in rats exposed to antimony potassium tartrate; however, one study reported a decrease in female rats exposed to 45.69 mg Sb/kg/day (Poon et al. 1998) and the other reported an increase in rats exposed to 0.63 mg Sg/kg/day (Schroeder et al. 1970).

3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after oral exposure to antimony.

Limited information on the immunotoxicity of antimony is available in animals. In the thymus of rats exposed to antimony potassium tartrate for 13 weeks, increases in medullary volume were observed in males exposed to ≥0.56 mg Sb/kg/day and in females exposed to ≥6.13 mg Sb/kg/day; a decrease in

cortical volume was also observed in females exposed to ≥6.13 mg Sb/kg/day (Poon et al. 1998). The biological significance of these findings is not known.

3.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to antimony.

None of the available studies adequately examined the potential neurotoxicity of antimony following oral exposure. Acute- and intermediate-duration studies that included histological examination of major tissues and organs did not report treatment-related alterations in the brain (Hext et al. 1999; NTP 1992; Poon et al. 1998).

3.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to antimony.

Information on the reproductive toxicity of antimony in laboratory animals is limited to a series of experiments conducted by Omura et al. (2002). No significant alterations in sperm count, motility, or morphology or histological alterations of the testes were observed in rats and mice exposed to 1,000 mg Sb/kg/day as antimony trioxide or 10 mg Sb/kg/day as antimony potassium tartrate.

3.2.2.6 Developmental Effects

A case-control study examined the possible relationship between levels of metals in drinking water and neural tube defects and did not find a significant association for antimony (Longerich et al. 1991). Zheng et al. (2014) found significantly higher median umbilical cord antimony levels in women with adverse pregnancy outcomes, but did not find a statistically significant association between antimony and adverse pregnancy outcomes. See Table 3-4 for more information on these studies.

Decreases in growth on postnatal days (PNDs) 10–22 were observed in the pups of rats exposed to 0.7 mg Sb/kg/day during gestation and lactation (Rossi et al. 1987); a decrease in maternal body weight gain was also observed at these doses. No differences in the number of newborn pups per litter or macroscopic teratogenic effects were observed in the offspring of rats treated during gestation with 0.7 mg Sb/kg/day as antimony trichloride (Rossi et al. 1987).

Studies by Angrisani et al. (1988) and Rossi et al. (1987) (data from both studies were also reported in Marmo et al. 1987) suggest that antimony may interfere with the normal development of the cardiovascular system. Alterations in vasomotor reactivity were observed in 30- and 60-day-old pups exposed during gestation and/or lactation and from weaning to PND 60; the estimated dose during the postnatal period was 0.1 mg Sb/kg/day. However, no alterations in arterial blood pressure were observed. Although the investigators describe this as altered development, comparisons were not made between the vasomotor responses in mature rats and in pups.

3.2.2.7 Cancer

Two epidemiology studies evaluated the possible association between antimony and cancer incidence (see Table 3-4). Colak et al. (2015) found a positive association between antimony levels in drinking water samples and cancer incidence among populations of three Turkish cities; the antimony levels in the water were <20 μg/L. Mendy et al. (2012) did not find a significant association between urinary antimony levels and self-reported cancer among adult NHANES participants.

No alterations in neoplastic lesion incidence were observed in rats (Schroeder et al. 1970) or mice (Kanisawa and Schroeder 1969) exposed 0.63 or 0.35 mg Sb/kg/day, respectively, as antimony potassium tartrate in drinking water for a lifetime. The use of these studies to assess carcinogenicity is limited because only one exposure level was used, which was below the maximum tolerated dose.

3.2.3 Dermal Exposure

The dermal toxicity of antimony compounds is discussed below. Data were located on the health effects following application of antimony trioxide, antimony thioantimonate (a mixture of antimony trisulfide and antimony pentasulfide), and antimony oxide to the skin or eye or following dermal or ocular contact with airborne antimony dust.

3.2.3.1 Death

No studies were located regarding death in humans after dermal exposure to antimony.

In a repeated exposure study, three of eight rabbits died due to exposure to antimony trioxide in an artificial sweat paste for 5–8 treatments; the remaining animals received 21 treatments and survived (Fleming 1982). Since the application area was not occluded, it is likely that the animals ingested the

paste. Damage to the cardiac portion of the stomach was noted in two of the three rabbits that died. No antimony-related deaths were reported in rabbits exposed to 3.3% antimony as antimony thioantimonate in calcium cup grease for 13 weeks (Horton et al. 1986).

3.2.3.2 Systemic Effects

Respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, dermal, and ocular effects following dermal or ocular exposure are presented below. No studies were located regarding musculoskeletal or body weight effects in humans and animals following dermal exposure to antimony. The highest NOAEL for each antimony compound and all reliable LOAEL values for each systemic effect for each species are recorded in Table 3-5; the results of the Fleming (1982) study was not included in the LSE table since it is very likely that the animals ingested large amounts of the antimony trioxide paste.

Respiratory Effects. No studies were located regarding respiratory effects in humans following dermal exposure to antimony. Hyperemia in the lungs was observed in a rabbit that died after six or eight applications of an antimony trioxide paste to shaven and abraded skin. The antimony trioxide (concentration not reported) was combined with a mixture resembling acidic sweat (Fleming 1982). The application area was not occluded; thus, the ingestion of the paste likely occurred.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following dermal exposure to antimony. Application of 3.3% antimony as antimony thioantimonate in calcium cup grease did not result in alterations in EKG readings or heart pathology in rabbits (Horton et al. 1986).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans following dermal exposure to antimony. Hemorrhages in the cardiac portion of the stomach were observed in a rabbit that died after six or eight applications of an antimony trioxide-acidic sweat paste (Fleming 1982). Because the application area was not occluded, ingestion of the paste is possible.

Hematological Effects. No studies were located regarding hematological effects in humans following dermal exposure to antimony. No alterations in hematological indices were observed in rabbits exposed to 3.3% antimony as antimony thioantimonate for 13 weeks (Horton et al. 1986).

Table 3-5. Levels of Significant Exposure to Antimony – Dermal

Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL	Less serious LOAEL	Serious LOAEL	Results	Reference/comments
ACUTE EXPOSURE								
Systemic Effects								
Rabbit 8M	Once; 0 or 20,900 mg Sb	CS	Dermal	20,900 mg Sb			No evidence of skin irritation.	Gross et al. 1955 (antimony trioxide)
Rabbit 10M	Once; 0 or 84 mg Sb	BW, OF, BI	Ocular	84 mg Sb			No evidence of eye irritation.	Gross et al. 1955 (antimony trioxide)
Rabbits (NS) 12 NS	Once 0 or 0.066 g Sb,	CS	Ocular		0.066 g Sb		Eye irritation consisting of conjunctival erythema, chemosis, and discharge 24 hours post-exposure. Superficial corneal injury in 4/12 rabbits 7-days post exposure.	Horton et al. 1986 (antimony thioantimonate)
Rat (Sprague Dawley) 5M, 5F	30 minutes 0, 122, 799, 1,395 mg Sb/m^3	CS, BW, GN, HP	Ocular	122 mg Sb/m^3	799 Mg Sb/m^3		Eye irritation and closure.	Price et al. 1979 (Stibine)
Guinea pig (Hartley) 5M, 5F	30 minutes 0, 122, 799, 1,395 mg Sb/m^3	CS, BW, GN, HP	Ocular	1395 mg Sb/m^3			No signs of eye irritation were reported.	Price et al. 1979 (Stibine)
Immunological and Lymphoreticular Effects								
Guinea pigs (Hartley) 10F	4 times 0 or 6.6% Sb,	CS		6.6% Sb			Negative in skin sensitization test.	Horton et al. 1986 (antimony thioantimonate)
INTERMEDIATE EXPOSURE								
Systemic Effects								
Rabbits (New Zealand white) 10M, 10F	6 hours/day 5 days/week 13 weeks 0, 0.33, and 3.3% Sb	LE, CS, BW, OF, HE, HP	Cardio Hepatic Renal Dermal Bd wt	3.3 3.3 3.3 3.3 3.3 %Sb			No treatment related alterations in histopathology, EKG measurements, hematology, clinical chemistry, or body weight.	Horton et al. 1986 (antimony thioantimonate)
Rat (Fischer 344) 50M, 50F	6 hours/day 5 days/week 13 weeks 0, 0.21, 0.902, 4.92, and 19.60 mg Sb/m^3	CS, BW, OP, HE, BI, HP	Ocular		0.21 mg Sb/m^3		Non-concentration-related increases in corneal irregularities were observed (approximately 30% in each group).	Newton et al. 1994 (antimony trioxide)

Table 3-5. Levels of Significant Exposure to Antimony – Dermal

Species (strain) No./group	Exposure parameters/ concentrations	Parameters monitored	System	NOAEL	Less serious LOAEL	Serious LOAEL	Results	Reference/comments
Reproductive Effects								
Rabbits (New Zealand white) 10M, 10F	6 hours/day 5 days/week 13 weeks 0, 0.33, and 3.3% Sb	LE, CS, BW, OF, HE, HP		%Sb			No histopathological alterations in the testes were reported.	Horton et al. 1986 (antimony thioantimonate)
CHRONIC EXPOSURE			3.3					
Systemic Effects								
Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks 0 or 36 mg Sb/m^3	LE, CS, BW, GN, HP	Dermal Ocular	36 36 mg Sb/m^3			No dermal or ocular effects were observed.	Groth et al. 1986 (antimony trioxide)
Rat (Wistar) 90M, 90F	7 hours/day 5 days/week 52 weeks 0 or 17.5 mg Sb/m^3	LE, CS, BW, GN, HP	Dermal Ocular	17.5 17.5 mg Sb/m^3			No dermal or ocular effects were observed.	Groth et al. 1986 (antimony ore)
Rat (Fischer 344) 65M, 65F	6 hours/day 5 days/week 12 months 0, 0.05, 0.43, and 3.8 mg Sb/m^3	CS, BW, OP, HE, BI, HP	Ocular	0.05 mg Sb/m^3	0.43 mg Sb/m^3		Increased incidence of cataracts at the end of the 12-month recovery period at ≥0.43 mg Sb/m^3.	Newton et al. 1994 (antimony trioxide)
Rat (Wistar Han) 50M, 50F	6 hours/day 5 days/week 2 years 0, 2.5, 8.3, and 25 mg Sb/m^3	CS, LE, BW, GN, HP	Dermal	8.3 mg Sb/m^3	25 mg Sb/m^3		Chronic inflammation and ulcers (females only) of the skin at 25 mg Sb/m^3.	NTP 2016 (antimony trioxide)
Mouse (B6C3F1) 50M, 50F	6 hours/day 5 days/week 2 years 0, 2.5, 8.3, and 25 mg Sb/m^3	CS, LE, BW, GN, HP	Dermal Ocular	25 25 mg Sb/m^3			No dermal or ocular effects were noted.	NTP 2016 (antimony trioxide)

Parameters monitored: BI = biochemical changes; BW = body weight; CS= clinical signs; DX = developmental toxicity; FI = food intake; GN = gross necropsy; HE = hematology; HP = histopathology; LE = lethality; OF = organ function; OP = ophthalmology; OW = organ weight

Bd wt = body weight; Cardio = cardiovascular; F = female(s); M = male(s); NS = not specified; Sb = antimony

Hepatic Effects. No studies were located regarding hepatic effects in humans following dermal exposure to antimony. No alterations in serum clinical chemistry parameters or histopathology of the liver were observed in rabbits exposed to 3.3% antimony as antimony thioantimonate for 13 weeks (Horton et al. 1986).

Renal Effects. No studies were located regarding renal effects in humans following dermal exposure to antimony. Increases in blood urea nitrogen and creatinine levels were observed in male rabbits exposed to 3.3% antimony as antimony thioantimonate; however, the levels were within the normal species variation and no histological alterations were observed in the kidneys (Horton et al. 1986).

Dermal Effects. Several studies have reported dermatitis in workers exposed to airborne antimony dust (Potkonjak and Pavlovich 1983). The dermatitis associated with exposure to airborne antimony is characterized as epidermal cellular necrosis with associated acute inflammatory cellular reactions (Stevenson 1965). The dermatitis is seen more often during the summer months and in workers exposed to high temperatures (Potkonjak and Pavlovich 1983; Stevenson 1965). Stevenson (1965) concluded that the dermatitis resulted from the action of antimony trioxide on the dermis after dissolving in sweat and penetrating the sweat glands. Transferring the worker to a cooler environment often resulted in the rash clearing up within 3–14 days. Antimony trioxide is not a skin sensitizer in humans following topical application (see Section 3.2.3.3).

In general, animal studies involving exposure to airborne antimony have not reported dermal effects (Groth et al. 1986; Newton et al. 1994). In a 13-week rat study (Newton et al. 1994 as reported in Bio/Dynamics 1985), alopecia was observed in females exposed to 0.902 or 4.11 mg Sb/m^3, but not females exposed to 19.60 mg Sb/m^3 or in males. Additionally, alopecia was not observed in a 1-year study conducted by this group (Newton et al. 1994). An intermediate-duration dermal exposure study did not report antimony-related skin irritation in rabbits exposed to 3.3% antimony as antimony antimonite (Horton et al. 1986); hyperkeratosis was observed in the vehicle control and antimony groups at similar incidences.

Ocular Effects. Eye irritation was reported in 27.5% of workers at an antimony smelter; it is unclear if this was due to antimony oxides or other constituents in the smelter dust (Potkonjak and Pavlovich 1983).

Several animal studies provide evidence that antimony is an ocular irritant. Eye irritation and closure were observed in rats exposed to ≥799 mg Sb/m^3 as stibine gas (Price et al. 1979); eye irritation was not noted in similarly exposed guinea pigs (Price et al. 1979). Exposure to airborne antimony trioxide resulted in corneal opacities in rats exposed to ≥0.21 mg Sb/m^3 for 13 weeks (Newton et al. 1994) and cataracts (focal posterior cataracts, posterior subcapsular cataracts, and complete cataracts) were observed in rats exposed to ≥0.43 mg Sb/m^3 for 1 year followed by a 1-year recovery period (Newton et al. 1994). An increase in the incidence of chromodacryorrhea was also observed in the chronic study; the investigators suggested that this may have been secondary to dental abnormality, infectious disease, or xerosis. Instillation of 0.066 g antimony as antimony thioantimonate into the eyes of rabbits resulted in eye irritation (Horton et al. 1986).

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following dermal exposure to antimony.

In a skin sensitization assay, 6.6% antimony as antimony thioantimonate in liquid petrolatum did not result in sensitization in guinea pigs (Horton et al. 1986). When the antimony thioantimonate was administered in calcium cup grease, a positive result for sensitization was found; however, this was likely due to the vehicle, since no reaction was found when antimony thioantimonate in petrolatum was used as the challenge agent (Horton et al. 1986).

No studies were located regarding the following effects in humans or animals after dermal exposure to antimony:

3.2.3.4 Neurological Effects
3.2.3.5 Reproductive Effects
3.2.3.6 Developmental Effects
3.2.3.7 Cancer

3.2.4 Other Routes of Exposure

Trivalent and pentavalent antimony compounds have been used for the treatment of parasitic diseases, particularly leishmaniasis and schistosomiasis, for over 100 years. Although trivalent antimony in the form of potassium or sodium antimony tartrate was first used, it was later discontinued due to the side effects. Pentavalent organic antimony compounds have been used for the last 60 years. The two

predominant forms are sodium antimony gluconate (sodium stibogluconate) and meglumine antimoniate (*N*-methyl-D-glucamine or Glucantime) (Haldar et al. 2011). In the treatment of parasitic diseases, the patient receives multiple injections of the antimony compounds. Numerous investigators have reported adverse effects associated with these treatments. These studies provide useful information for identifying potential targets of antimony toxicity, although the relevance to environmental exposure is not known given the poor absorption of antimony compounds following inhalation, oral, or dermal exposure (see Section 3.4.1). The primary targets of toxicity appear to the heart (alterations in EKG readings), gastrointestinal tract (nausea, abdominal pain, vomiting, diarrhea, anorexia), musculoskeletal system (myalgia, arthralgia), liver (increases in alanine and aspartate aminotransferases), pancreas (increases in serum amylase levels), and nervous system (headache, dizziness) (Andersen et al. 2005; Dancaster et al. 1966; Lawn et al. 2006; Neves et al. 2009; Palacios et al. 2001; Sundar et al. 1998; Thakur 1998; Zaki et al. 1964). Alterations in electrocardiograms, particularly prolongation of QT interval, have been reported following injection of sodium antimony tartrate (Honey 1960), sodium antimony gluconate (Dancaster et al. 1966; Lawn et al. 2006; Sundar et al. 1998; Thakur 1998), and meglumine antimoniate (Neves et al. 2009). Whereas a very high incidence was reported in patients treated with sodium antimony tartrate (98%, with 30% categorized as severe EKG changes) (Honey 1960), a much lower incidence (8–25%) was found in patients treated with pentavalent antimony (Dancaster et al. 1966; Neves et al. 2009). The cardiotoxicity of antimony (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966) and the differences in the cardiotoxicity of trivalent and pentavalent antimony (Alvarez et al. 2005) are supported by animal studies. Whereas intramuscular injections of 16 mg Sb/kg/day as meglumine antimoniate for 26 days resulted in a slight prolongation of the QT duration in guinea pigs, intramuscular administration of 10 mg Sb/kg/day as antimony potassium tartrate for 8–12 days resulted in bradycardia and a more marked elongation of the QT interval (Alvarez et al. 2005).

Significant decreases in blood glucose levels were observed in rats exposed to 900 mg Sb/kg/day as stibogluconate or 300 or 900 mg Sb/kg/day meglumine antimoniate administered via intramuscular injections for 30 days (Alkhawajah et al. 1992); the investigator did not note whether the animals were fasted prior to measurement of blood glucose levels.

Three studies have evaluated the developmental toxicity of pentavalent antimony. Subcutaneous administration of 300 mg Sb/kg as meglumine antimoniate or intramuscular administration of 100 or 300 mg Sb/kg/day as sodium stibogluconate or meglumine antimoniate to rats during gestation or during gestation and lactation resulted in decreases in birth weight and number of viable offspring (Alkhawajah et al. 1996; Coelho et al. 2014a; Miranda et al. 2006). Intramuscular administration of 100 mg Sb/kg/day

as antimony trichloride also resulted in decreases in viable fetuses and fetal body weight (Alkhawajah et al. 1996). Increases in resorptions were also observed in rats administered ≥100 mg Sb/kg/day as sodium stibogluconate, meglumine antimoniate, or antimony trichloride (Alkhawajah et al. 1996). Miranda et al. (2006) also found a significant increase in dilated ureters following gestation exposure; no other external or visceral abnormalities were found. No alterations in neurological development or sperm counts were observed in offspring exposed during gestation and lactation (Coelho et al. 2014a).

3.3 GENOTOXICITY

The genotoxicity of trivalent and pentavalent antimony has been evaluated in *in vivo* studies in humans, rats, and mice and in *in vitro* studies in bacterial and mammalian systems. As summarized in Table 3-6, most studies of antimony trioxide did not find clastogenic alterations in orally exposed (gavage administration) rats or mice (Elliott et al. 1998; Gurnani et al. 1992a, 1992b; Kirkland et al. 2007). One study (Gurnani et al. 1992a, 1993) found significant increases in chromosomal aberrations in mice bone marrow cells following repeated exposure to antimony trioxide; no significant alterations were found following a single exposure. However, other studies testing similar doses did not find increases in chromosomal aberrations (Kirkland et al. 2007) or micronuclei formation (Elliott et al. 1998; Kirkland et al. 2007) following repeated exposure. One occupational exposure study of workers exposed to a flame retardant containing antimony trioxide did not find increases in the occurrence of micronuclei or sister chromatid exchange (Cavallo et al. 2002). Two studies of pentavalent organic antimony found positive results for micronuclei formation (Hantson et al. 1996; Lima et al. 2010) or DNA damage (Lima et al. 2010).

The results of *in vitro* genotoxicity studies are presented in Table 3-7. In general, no alterations in the occurrence of gene mutations were found in bacterial assays testing metallic antimony (Asakura et al. 2009), antimony trioxide (Elliott et al. 1998; Kuroda et al. 1991), antimony trichloride (Kubo et al. 2002; Kuroda et al. 1991), antimony pentachloride (Kuroda et al. 1991), or antimony pentoxide (Kuroda et al. 1991) or in mammalian assays with antimony thioantimonate (Tu and Sivak 1984) or antimony trioxide (Elliott et al. 1998). Evidence of DNA damage was observed for antimony trioxide, antimony trichloride, and antimony pentachloride in rec assays with *Bacillus subtilis* (Kanematsu et al. 1980; Kuroda et al. 1991). Unlike the *in vivo* data, most studies found increases in the occurrence of chromosomal aberrations (Asakura et al. 2009; Elliott et al. 1998; Paton and Allison 1972; Tu and Sivak 1984), micronuclei formation (Gebel et al. 1998a; Huang et al. 1998; Migliore et al. 1999; Schaumlöffel and

Table 3-6. Genotoxicity of Antimony *In Vivo*

End point	Species (test system)	Results	Reference	Compound
Chromosomal aberrations	Human peripheral lymphocytes (intramuscular)	–	Hantson et al. 1996	Meglumine antimonate
	Mouse bone marrow; single exposure (gavage)	–	Gurnani et al. 1992a, 1992b	Antimony trioxide
	Mouse bone marrow; 7–21 exposures (gavage)	+	Gurnani et al. 1992a, 1993	Antimony trioxide
	Rat bone marrow; single exposure (gavage)	–	Kirkland et al. 2007	Antimony trioxide
	Rat bone marrow; 7–21 exposures (gavage)	–	Kirkland et al. 2007	Antimony trioxide
Micronuclei formation	Human peripheral lymphocytes (inhalation)	–	Cavallo et al. 2002	Antimony trioxide
	Human peripheral lymphocytes (intramuscular)	+	Hantson et al. 1996	Meglumine antimonate
	Mouse bone marrow (gavage)	+	Lima et al. 2010	N-Methyl-glucamine antimonate
	Mouse bone marrow; single exposure (gavage)	–	Elliott et al. 1998	Antimony trioxide
	Mouse bone marrow; 7–21 exposures (gavage)	–	Elliott et al. 1998	Antimony trioxide
	Rat bone marrow; single exposure (gavage)	–	Kirkland et al. 2007	Antimony trioxide
	Rat bone marrow; 7–21 exposures (gavage)	–	Kirkland et al. 2007	Antimony trioxide
Sister chromatid exchange	Human peripheral lymphocytes (inhalation)	–	Cavallo et al. 2002	Antimony trioxide
	Human peripheral lymphocytes (intramuscular)	–	Hantson et al. 1996	Meglumine antimonate
DNA damage	Mouse peritoneal macrophages (gavage)	+	Lima et al. 2010	N-Methyl-glucamine antimonate
DNA repair	Rat liver (gavage)	–	Elliott et al. 1998	Antimony trioxide
Sperm head abnormalities	Mouse sperm (gavage)	–	Gurnani et al. 1992a, 1993	Antimony trioxide

– = negative result; + = positive result; DNA = deoxyribonucleic acid

Table 3-7. Genotoxicity of Antimony *In Vitro*

End point	Species (test system)	Results: With activation	Results: Without activation	Reference	Compound
Prokaryotic organisms					
Gene mutation	*Salmonella typhimurium*				
	TA100, TA1535, TA98, TA1537 (reverse mutation)	–	+[a]	Asakura et al. 2009	Metallic antimony
	TA100, TA1535, TA1537, TA98 (plate incorporation)	–	–	Elliott et al. 1998	Antimony trioxide
	TA100, TA98 (Ames test)	–	–	Kubo et al. 2002	Antimony trichloride
	TA100, TA98 (plate incorporation)	–	–	Kuroda et al. 1991	Antimony trichloride
	TA100, TA98 (plate incorporation)	–	–	Kuroda et al. 1991	Antimony pentachloride
	TA100, TA98 (plate incorporation)	–	–	Kuroda et al. 1991	Antimony trioxide
	TA100, TA98 (plate incorporation)	–	–	Kuroda et al. 1991	Antimony pentoxide
	TA100, TA1535, TA97, TA98	–	–	Zeiger et al. 1992; NTP 1992	Antimony potassium tartrate
	Escherichia coli,				
	WP2uvrA/pKM101 (reverse mutation)	–	–	Asakura et al. 2009	Metallic antimony
	WP2P, WP2PuvrA (plate incorporation)	–	–	Elliott et al. 1998	Antimony trioxide
	PQ37 (SOS chemotest)	No data	–	Lantzsch and Gebel 1997	Antimony trichloride
DNA damage	*Bacillus subtilis* (rec assay)	No data	+	Kuroda et al. 1991	Antimony trioxide
		No data	+	Kuroda et al. 1991	Antimony trichloride
		No data	+	Kuroda et al. 1991	Antimony pentachloride
		No data	–	Kuroda et al. 1991	Antimony pentoxide
		No data	+	Kanematsu et al. 1980	Antimony trioxide
		No data	+	Kanematsu et al. 1980	Antimony trichloride
		No data	+	Kanematsu et al. 1980	Antimony pentachloride

Table 3-7. Genotoxicity of Antimony *In Vitro*

End point	Species (test system)	Results: With activation	Results: Without activation	Reference	Compound
Mammalian cells					
Gene mutation	Chinese hamster ovary cells (HGPRT locus)	–	–	Tu and Sivak 1984	Antimony thioantimonate
	L5178Y mouse lymphoma	–	–	Elliott et al. 1998	Antimony trioxide
Chromosomal aberrations	Human leukocytes	No data	+	Paton and Allison 1972	Antimony sodium tartrate
		+	+	Elliott et al. 1998	Antimony trioxide
	Chinese hamster ovary cells	+	+	Tu and Sivak 1984	Antimony thioantimonate
		+	+	Asakura et al. 2009	Metallic antimony
Micronuclei formation	Human bronchial epithelial cells (BES-6)	No data	+	Huang et al. 1998	Antimony trichloride
	Human fibroblasts	No data	+	Huang et al. 1998	Antimony trichloride
	Human lymphocytes	No data	+	Migliore et al. 1999	Potassium antimonate
	Human lymphocytes	No data	+	Schaumlöffel and Gebel 1998	Antimony trichloride
	V79 Chinese hamster cells	No data	+	Gebel et al. 1998a	Antimony trichloride
	Chinese hamster ovary cells	No data	+	Huang et al. 1998	Antimony trichloride
Sister chromatid exchange	V79 Chinese hamster ovary cells	No data	+	Kuroda et al. 1991	Antimony trichloride
		No data	+	Kuroda et al. 1991	Antimony trioxide
		No data	–	Kuroda et al. 1991	Antimony pentachloride
		No data	–	Kuroda et al. 1991	Antimony pentoxide

Table 3-7. Genotoxicity of Antimony *In Vitro*

End point	Species (test system)	Results		Reference	Compound
		With activation	Without activation		
DNA damage	Human lymphocytes (comet assay)	No data	–	Lima et al. 2010	N-Methyl-glucamine antimonate
	Human lymphocytes (comet assay)	No data	+	Schaumlöffel and Gebel 1998	Antimony trichloride
	V79 Chinese hamster cells (comet assay)	No data	+	Gebel et al. 1998a	Antimony trichloride

[a]Only positive for TA1537 strain.

– = negative result; + = positive result

Gebel 1998), and sister chromatid exchange (Kuroda et al. 1991) in mammalian cells exposed to trivalent antimony compounds or metallic antimony. Pentavalent antimony compounds were negative in sister chromatid exchange assays (Kuroda et al. 1991). Similarly, DNA damage was observed in mammalian cells exposed to antimony trichloride (Gebel et al. 1998a; Schaumlöffel and Gebel 1998), but negative for pentavalent organic antimony (Lima et al. 2010).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Inhaled antimony particles that deposit in the respiratory tract are subject to three general distribution processes: (1) bronchial and tracheal mucociliary transport to the gastrointestinal tract; (2) transport to thoracic lymph nodes (e.g., lung, tracheobronchial, mediastinal); or (3) absorption into blood and/or lymph and transfer to other tissues (e.g., peripheral lymph tissues, liver, kidney). The above processes apply to all forms of deposited antimony, although the relative contributions of each pathway and rates associated with each pathway vary with the physical characteristics (e.g., particle size, solubility).

Particles having diameters >5 μm deposit in the upper airways (extrathoracic, tracheobronchial regions) and are cleared from the respiratory tract primarily by mucociliary transport to the gastrointestinal tract. Smaller particles (≤5 μm, *respirable* particles) are deposited primarily in the pulmonary region (terminal bronchioles and alveoli). Particles are cleared from the pulmonary region primarily by absorption, lymph drainage, macrophage phagocytosis and migration, and upward mucociliary flow. Total alveolar clearance is mediated largely by alveolar macrophages, primarily via migration of particle-laden macrophages to the ciliated airways and to a lesser extent via penetration through the interstitium to the pulmonary lymphatic system (Yu and Rappaport 1996). Exposure to 1.6 μm particles of antimony tartrate resulted in a greater deposition of antimony in the upper respiratory tract than exposure to 0.7 or 0.3 μm particles (Felicetti et al. 1974a; Thomas et al. 1973). Furthermore, the antimony deposited in the upper respiratory tract was cleared after several hours via mucociliary clearance. Particles of the two smaller sizes were relatively insoluble in the lung and were slowly absorbed over several weeks (Thomas et al. 1973). No valence-specific difference in the body burden was observed 1 day after exposure to trivalent or pentavalent antimony tartrate (Felicetti et al. 1974b).

Dissolved antimony is absorbed into blood; the rate of absorption will depend on solubility. The International Commission on Radiological Protection (ICRP 1981) considers oxides, hydroxides, halides, sulfides, sulfates, and nitrates of antimony to be class W chemicals. All other common compounds of antimony are assigned to class D. Class W and D chemicals are considered to have respiratory tract clearance rates of weeks and days, respectively. The ICRP classifications are based on animal data (Felicetti et al. 1974a, 1974b; Thomas et al. 1973). Data from deceased antimony smelter workers suggest that the elimination half-times of some forms of antimony in the lungs may be longer than weeks (Gerhardsson et al. 1982).

Using data from the Newton et al. (1994) 1-year study of rats exposed to several concentrations of antimony trioxide, Yu and Rappaport (1996) and Newton et al. (1994) found that the pulmonary clearance half-time increased with increasing antimony lung burdens. Clearance was significantly decreased at lung burdens of >0.11 mg (Yu and Rappaport 1996). In rats exposed to antimony trioxide for 1 year, Newton et al. (1994) estimated a pulmonary clearance time of 2 months in rats with a lung burden of 200 μg and 10 months in rats with a lung burden of 2,000 μg. In rats exposed to 0.06, 0.51, or 4.50 mg antimony trioxide/m^3 (ratio of 1:10:90), the lung burden ratios were 1:11:138. The decrease in clearance rates is likely due to antimony-specific impairment of alveolar macrophages (Yu and Rappaport 1996). As would be expected, lung burdens increased with exposure duration. In rats exposed for 90 days, there was an initial rapid accumulation phase, which lasted 2–4 weeks, followed by a second slower accumulation phase; there was no indication that lung accumulation reached steady state. However, a 1-year study showed that steady-state lung burden was reached after approximately 6 months of exposure to antimony trioxide (Newton et al. 1994).

3.4.1.2 Oral Exposure

No quantitative data on the absorption of antimony from the gastrointestinal tract in humans were located. However, results of studies in animals suggest that antimony is poorly absorbed from the gastrointestinal tract. Estimates of the absorption of antimony tartrate and antimony trichloride in animals range from 2 to 7% (Felicetti et al. 1974b; Gerber et al. 1982). A study of pentavalent antimony estimated a bioavailability of 10% in dogs administered via gavage a single dose of 100 mg antimony/kg as meglumine antimoniate (Ribeiro et al. 2010); the mean absorption time was 3.1 hours. Gastrointestinal absorption of antimony is likely to be affected by numerous factors, including chemical form of the ingested antimony, solubility, age, and diet. Although quantitative information on the absorption of antimony is not available for all forms, ICRP (1981) has recommended 10% for antimony tartrate and 1%

for all other forms of antimony as reference values for gastrointestinal absorption in humans. A dog study (Ribeiro et al. 2010) showed that maximum blood concentration was reached 0.89 hours after gavage administration of 100 mg Sb/kg as meglumine antimoniate.

The gastrointestinal absorption of antimony may be saturable. A comparison of blood concentrations 24 hours after administration of 100 or 1,000 mg/kg antimony trioxide found only a 2-fold difference, even though there was a 10-fold difference in doses (Kirkland et al. 2007).

3.4.1.3 Dermal Exposure

No studies were located regarding absorption of antimony in humans following dermal exposure.

Exposure to high levels of antimony trioxide or a mixture of antimony trioxide and pentoxide resulted in death in rabbits (Myers et al. 1978). Since the application area was occluded, the study suggests that at least some forms of antimony can be absorbed through the skin.

3.4.2 Distribution

Very low levels of antimony are found in unexposed humans. Autopsy data on Japanese adults (Sumino et al. 1975) and other data on selected body fluids are presented in Table 3-8. The mean body burden of antimony was 0.7 mg (Sumino et al. 1975). The skin and hair had the highest levels of antimony. A somewhat higher estimate of 7.9 mg for total body burden is reported by ICRP (1981). ICRP (1981) has recommended reference values of 5.9 mg of antimony in soft tissue and 2.0 mg in skeletal tissue.

Studies of antimony concentrations in the liver and kidneys of dogs, cats, and horses exposed to background antimony found no differences in liver or kidney antimony concentrations in dogs and cats (Paßlack et al. 2014b, 2014c), but found that the liver antimony levels were significantly higher than kidney levels in horses (Paßlack et al. 2014a). No sex- or age-related differences in antimony concentrations were found (Paßlack et al. 2014a, 2014b, 2014c). In dogs and cats, chronic kidney disease did not appear to influence the antimony levels in the liver or kidneys (Paßlack et al. 2014b, 2014c).

Table 3-8. Background Levels of Antimony Found in Various Tissues of Humans

Tissue	Mean concentration (µg/g) ± standard deviation	Reference
Hair	0.12±0.18	Muramatsu and Parr 1988
	0.096	Takagi et al. 1986
Adrenal gland	0.073±0.14	Sumino et al. 1975
Skin	0.096±0.10	Sumino et al. 1975
Lung	0.062±0.056	Sumino et al. 1975
Large intestine	0.047±0.062	Sumino et al. 1975
Trachea	0.045±0.031	Sumino et al. 1975
Cerebellum	0.030±0.032	Sumino et al. 1975
Kidney	0.043±0.041	Sumino et al. 1975
	Not detected	Muramatsu and Parr 1988
Small intestine	0.039±0.044	Sumino et al. 1975
Heart	0.032±0.038	Sumino et al. 1975
Pancreas	0.030±0.029	Sumino et al. 1975
Spleen	0.029±0.025	Sumino et al. 1975
Liver	0.023±0.026	Sumino et al. 1975
	Not detected	Muramatsu and Parr 1988
Cerebrum	0.017±0.024	Sumino et al. 1975
Blood	0.016±0.022	Sumino et al. 1975
	0.34±2.0	Mansour et al. 1967

3.4.2.1 Inhalation Exposure

Information on the distribution of antimony in humans following inhalation exposure was not located. Studies in hamsters demonstrate that the highest concentrations of antimony are found in the lungs, gastrointestinal tract, liver, kidney, and skeleton (Felicetti et al. 1974b). In hamsters, the levels of trivalent antimony increase more rapidly in the liver than pentavalent antimony. Skeletal uptake is greater following exposure to pentavalent antimony than trivalent antimony (Felicetti et al. 1974b). One day postexposure, the highest percentage of body burden is found in the gastrointestinal tract. Following exposure to trivalent antimony tartrate, antimony is also retained in the skin, liver, skeleton, and lung (in descending order). For pentavalent antimony, the highest percentage of body burden (outside of gastrointestinal tract) is skin, skeleton, and liver. Studies involving exposure to antimony trioxide, a relatively insoluble compound, demonstrate that most antimony is retained in the lungs (Newton et al. 1994).

The relative partitioning between erythrocytes and plasma is a function of valency. Following exposure to trivalent antimony, erythrocyte levels are elevated, compared to the elevated plasma antimony levels after inhalation exposure to pentavalent antimony (Felicetti et al. 1974b; Newton et al. 1994). In hamsters, the ratios of erythrocyte to plasma antimony levels were 1.14 for trivalent antimony and 0.29 for pentavalent antimony at exposure termination and 8.1 and 2.9, respectively, 1-day postexposure (Felicetti et al. 1974b). The clearance of antimony from the blood appears to differ among animal species. Elevated blood antimony levels persist longer in rats than in mice and dogs (Felicetti et al. 1974a; Thomas et al. 1973).

3.4.2.2 Oral Exposure

Data on the distribution of antimony in humans following oral exposure to antimony were not located.

Following oral exposure in animals, the major sites of accumulation, outside of the gastrointestinal tract, are the liver, kidney, bone, lung, spleen, and thyroid (Ainsworth et al. 1991; Kirkland et al. 2007; NTP 1992; Sunagawa 1981). In rats exposed to antimony potassium tartrate for 13 weeks, the highest concentration of antimony was found in the red blood cells, followed by the spleen, liver, kidney, brain and fat, and serum (Poon et al. 1998). Neither NTP (1992) nor Sunagawa (1981) reported dose-related increases in tissue antimony levels; however, Poon et al. (1998) reported apparent dose-related increases in kidney, liver, spleen, and red blood cell antimony levels. This lack of dose-responsiveness may be a reflection of decreased absorption at higher antimony concentrations or may represent saturation in some

tissues. Antimony levels tend to reach a plateau in the livers and lungs of voles fed a diet containing antimony trioxide (Ainsworth et al. 1991). In rats exposed to antimony potassium tartrate in drinking water for 16 days (NTP 1992) or 13 weeks (Poon et al. 1998) or antimony trioxide once or 3 times in an 8-day period (Kobayashi and Ogra 2009), the blood had the highest concentration of antimony. The antimony levels in blood were 3 times higher than the levels in the kidney, heart, spleen, and liver (NTP 1992). In the blood, pentavalent antimony is primarily found in the serum of dogs administered 100 mg antimony/kg as meglumine antimoniate (Ribeiro et al. 2010); trivalent antimony was found primarily in the red blood cells of rats exposed to antimony potassium tartrate for 90 days (Poon et al. 1998) or antimony trioxide once or 3 times (Kobayashi and Ogra 2009).

Evidence is insufficient to determine if there are valency differences in the distribution of orally administered antimony. A study of rats exposed to similar concentrations of metallic antimony and antimony trioxide found some differences (Sunagawa 1981). Similar antimony concentrations were found in the liver and blood of rats exposed to metallic antimony compared to a 10-fold higher concentration in the blood compared to the liver in rats exposed to antimony trioxide.

There are limited data on the maternal transfer of antimony following oral exposure. Elevated antimony levels were found in the pups of rat dams fed radiolabeled antimony chloride (exact compound not reported) during pregnancy and lactation (Gerber et al. 1982). The highest activities (in descending order) were detected in the bone, muscle, spleen, heart, kidney, and lung. After exposure termination, antimony levels rapidly declined, with a half-life of approximately 10 days. When *in utero* exposed pups were cross-fostered to controls, antimony levels were maintained. In control newborns cross-fostered to antimony dams, there was a rapid increase in antimony level, reaching 80% of the levels of pups exposed during gestation and lactation.

3.4.2.3 Dermal Exposure

No information on the distribution of antimony in humans or animals following dermal exposure to antimony was located.

3.4.2.4 Other Routes of Exposure

No information on the distribution of antimony in humans following parenteral exposure was located. In animals, antimony is recovered primarily in the liver, with smaller amounts in the spleen, heart, lungs, and muscle (Gellhorn et al. 1946; Gerber et al. 1982).

As discussed in the inhalation and oral exposure sections, trivalent antimony is incorporated into the erythrocytes, mainly in the hemoglobin fraction (Edel et al. 1983; Lippincott et al. 1947) and pentavalent antimony is primarily distributed into the plasma fraction of blood (Edel et al. 1983).

Following intraperitoneal administration of trivalent antimony compounds, the concentration of antimony in the liver exceeded the antimony concentration in the spleen (Gellhorn and van Dyke 1946). In contrast, administration of pentavalent antimony compounds resulted in spleen concentrations that exceeded the liver concentration. Similarly, a 21-day subcutaneous administration of 300 mg antimony/kg as meglumine antimoniate (pentavalent antimony) to rats resulted in the highest antimony concentrations in the spleen; high levels were also found in the kidneys, femur, thyroid, and liver (Coelho et al. 2014b). The antimony concentration in the spleen was at least 4–5 times higher than in other tissues; the concentrations in the kidneys, femur, and thyroid were similar and about 2 times higher than in the liver. Twenty-one days after the last exposure, the highest concentration was found in the spleen followed by the femur and thyroid (similar concentrations), lungs, adrenals, kidneys, and liver (Coelho et al. 2014b). In contrast, intraperitoneal administration of antimony potassium tartrate (1.5–11 mg/kg/day) to rats for 16 days resulted in the highest antimony concentration in the blood, followed by the liver, spleen, heart, and kidney (NTP 1992). At the lower doses, the liver and spleen had similar concentrations, which were 2 times higher than the heart and kidney levels. Following a 13-week exposure to 24 mg/kg/day, the blood antimony concentration was >2 times higher than the spleen levels; the spleen had 20% more antimony than the liver, and the heart and kidney had similar concentrations that were approximately 10-fold lower than blood.

A series of experiments in which rat dams were administered subcutaneous injections of 300 mg pentavalent antimony/kg/day as meglumine antimoniate during gestation and/or lactation demonstrates maternal-fetal and maternal-infant transfer of antimony (Coelho et al. 2014a). The levels of antimony in the blood of the offspring were approximately 44, 60, 77, and 135% of maternal blood levels when antimony was administered on gestation days (GDs) 0–20, GD 0 through PND 13, PNDs 1–13, and PNDs 5–19, respectively.

3.4.3 Metabolism

Antimony is a metal and, therefore, does not undergo metabolism. Antimony can covalently interact with sulfhydryl groups and phosphate, as well as numerous reversible binding interactions with endogenous

ligands (e.g., proteins). It is not known if these interactions are toxicologically significant. There are limited data on the *in vivo* conversion of pentavalent antimony to trivalent antimony. In humans administered Ulamina (an experimental drug containing antimony pentachloride and N-methyl-glucamine) via intramuscular injection, 23% of the pentavalent antimony was converted to trivalent antimony (Vasquez et al. 2006).

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Increased levels of urinary antimony have been noted in workers exposed to antimony trioxide (Cooper et al. 1968; Ludersdorf et al. 1987). In animals, antimony is excreted via the urine and feces. Some of the fecal antimony may represent unabsorbed antimony that is cleared from the lung via mucociliary action into the esophagus to the gastrointestinal tract. Antimony is excreted predominantly in the urine following pentavalent antimony injection and in the feces after trivalent antimony administration (Edel et al. 1983; Felicetti et al. 1974b).

The whole-body clearance of trivalent or pentavalent antimony tartrate in hamsters is biphasic. One day postexposure, 65 and 60% of the initial body burden of trivalent and pentavalent antimony, respectively, was excreted (Felicetti et al. 1974b). The half-life of the slow phase was approximately 16 days.

3.4.4.2 Oral Exposure

Information on the excretion of antimony in humans following oral exposure was not located. However, information obtained from human and animal studies in which antimony was administered parenterally provides some insight regarding the routes and rates of excretion that can be anticipated after oral exposure in humans. Animal studies have shown that ingested antimony is only partially absorbed from the gastrointestinal tract (Felicetti et al. 1974b; Gerber et al. 1982). Assuming that this is also true for humans, fecal excretion is probably an important route of excretion of ingested antimony in humans. Antimony absorbed from the gastrointestinal tract appears to be excreted in the urine and feces to a variable degree, depending on the chemical form.

3.4.4.3 Dermal Exposure

No information on the excretion of antimony following dermal exposure in humans or animals was located.

3.4.4.4 Other Routes of Exposure

Pentavalent antimony is rapidly excreted in humans following intravenous or intramuscular administration, with >50% excreted in the urine 6 hours after injection (Goodwin and Page 1943; Rees et al. 1980). Trivalent antimony is predominantly excreted in the feces and not as rapidly excreted in the urine as pentavalent antimony. Twenty-four hours after injection, approximately 25% was excreted in the urine (Goodwin and Page 1943).

Following repeated intramuscular administration of trivalent antimony in humans, approximately 15% was excreted per day at the beginning of treatment and 25% at the end of treatment. Fecal antimony excretion ranged from 4% in the beginning of treatment to 15.4% of the daily administered dose toward the end of treatment (Lippincott et al. 1947).

Twenty-four hours following intraperitoneal administration of trivalent antimony in rats, 33% of the compound was excreted via the feces and 6% in the urine. In contrast, 88% of the pentavalent antimony was excreted in the urine and 1% in the feces (Edel et al. 1983). Another study found that 45–55% of the antimony administered via intravenous or intraperitoneal administration of antimony trichloride was excreted in the urine or feces within 4 days (Bailly et al. 1991). Route-specific differences in the excretion routes were found. Following intraperitoneal injection, the amount of antimony in the feces was 4 times higher than the amount in the urine; in contrast, the amount in urine and feces was similar when administered via intravenous administration. Antimony was partially excreted in the bile likely bound to glutathione; some of the biliary antimony was reabsorbed in the intestine via enterohepatic circulation (Bailly et al. 1991).

The elimination of pentavalent antimony following intramuscular injection fits into a two-compartment pharmacokinetic model. The half-life of the rapid phase of elimination was 2 hours (Chulay et al. 1988; Vasquez et al. 2006); the slower phase was 76 hours (Chulay et al. 1988). A more recent study that had a lower detection limit suggested that antimony elimination fits a three-compartment model; the terminal half-life was >30 days (Friedrich et al. 2012).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. However, if the uptake and disposition of the chemical substance(s) are adequately described, this simplification is desirable because data are often unavailable for many

biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

If PBPK models for antimony exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

No PBPK models for antimony were identified.

3.5 MECHANISMS OF ACTION

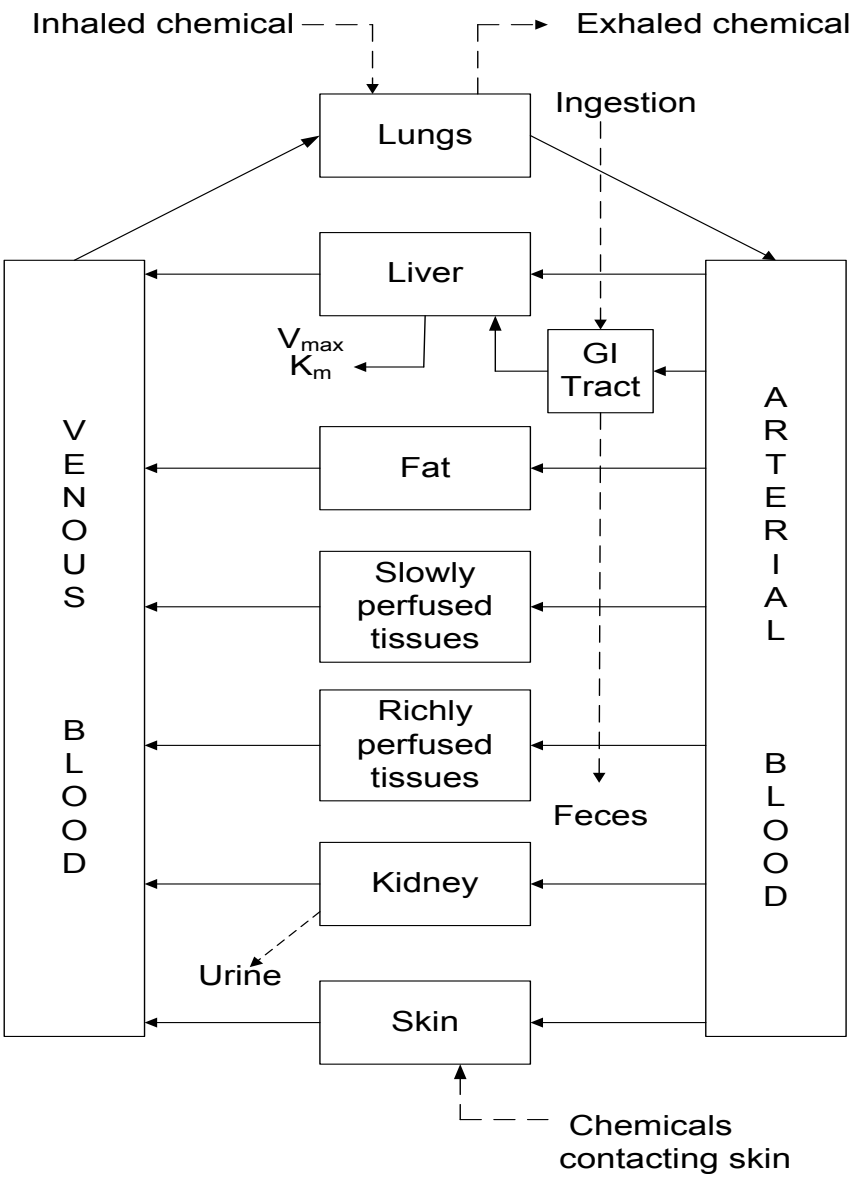
3.5.1 Pharmacokinetic Mechanisms

There are very limited data on pharmacokinetic mechanisms. Maciaszczyk-Dubinska et al. (2012) suggested that trivalent antimony can enter the cell via aquaglyceroporins, which are membrane proteins, because trivalent antimony in the trihydroxylated uncharged form resembles glycerol. There is also some evidence that trivalent antimony can enter the cell via hexose transporters. Sun et al. (2000) suggested that trivalent antimony forms a stable complex with glutathione, which provides a possible transport mechanism.

3.5.2 Mechanisms of Toxicity

Several *in vitro* studies have investigated the cardiotoxicity of antimony, particularly damage to the myocytes, which results in cell death and alterations and could lead to abnormalities in EKGs and arrhythmias. Tirmenstein (1995, 1997) found that exposure to antimony potassium tartrate resulted in several biochemical alterations in cardiac myocytes including the disruption of cellular thiol homeostasis, particularly the depletion of glutathione, induction of lipid peroxidation, and binding to vicinal thiols such as pyruvate dehydrogenase. The inhibition of pyruvate dehydrogenase subsequently leads to a decrease

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: Krishnan and Andersen 1994

in cellular ATP levels. These biochemical alterations all contribute to cell death. Additionally, exposure to antimony potassium tartrate disrupts calcium homeostasis in myocytes. Wey et al. (1997) found a progressive elevation of resting (or diastolic) transient calcium levels in myocytes and an eventual cessation of beating activity that preceded cell death. Further investigations by this group found that antimony potassium tartrate reduced calcium availability during excitation-contraction and that there was a decreased flux of calcium through voltage-dependent L-type calcium channels in the myocyte (Toraason et al. 1997). The decreased influx of calcium was likely due to enhanced removal of calcium (Toraason et al. 1997). The investigators noted that the reduced influx and enhanced efflux of calcium could account for the reduced cardiac output observed in *in vivo* studies. Another study found that trivalent antimony increased cardiac calcium currents, resulting in a prolonged action potential (Kuryshev et al. 2006). The prolonged action potential results in a delay in cardiac repolarization, which could explain the QT prolongation observed in EKGs and arrhythmias in humans administered antimony for the treatment of leishmaniasis (Kuryshev et al. 2006). Similar findings were observed in myocytes exposed to pentavalent antimony, although the investigators concluded that this was likely due to the conversion of pentavalent antimony to trivalent antimony. Pentavalent antimony also increased sodium current amplitude, which was not observed in trivalent antimony exposed myocytes. However, the change in sodium current amplitude was not likely to contribute to arrhythmia since it was not accompanied by any obvious changes in channel gating (Kuryshev et al. 2006).

3.5.3 Animal-to-Human Extrapolations

Overall, the available human and laboratory animal data suggest that the end points of antimony toxicity are similar across species. The primary effects observed in antimony workers are respiratory effects such as pneumoconiosis and evidence of heart damage. Lung damage is the primary effect reported in rats, mice, and rabbits exposed to airborne antimony trioxide. Additionally, parenteral administration studies in laboratory animals have found EKG alterations, which is a commonly reported side effect in humans receiving repeated injections of antimony compounds, particularly trivalent compounds, for the treatment of leischmaniasis. Although similar end points have been identified, there are limited data comparing the potency across species of antimony administered via environmentally relevant routes of exposure. NTP (2016) found species differences in the toxicity and carcinogenicity of antimony trioxide. Although rats and mice were exposed to the same concentrations, alveolar/bronchiolar carcinomas were observed in mice exposed to ≥2.5 mg Sb/m^3, but carcinomas were not observed in rats exposed to 2.5 or 25 mg Sb/m^3. This study also found differences in lung burdens between rats and mice. In rats, lung burdens appeared to reach steady state at lower concentrations (2.5 and 8.3 mg Sb/m^3); lung burden steady state was not

reached at any of the exposure concentrations in mice. In an NTP (1992) 13-week intraperitoneal injection study, antimony potassium tartrate was more toxic in rats than mice. Increases in mortality and hepatocellular degeneration and necrosis were observed in rats; no deaths or histopathological alterations were observed in mice administered the same dosages.

3.6 HAZARD IDENTIFICATION AND MINIMAL RISK LEVELS

3.6.1 Hazard Identification

Systematic review of the available human and animal studies that assessed the potential health effects associated with inhalation or oral exposure to antimony identified a number of potential targets of toxicity. Hazard identification conclusions were determined for the most sensitive end points (i.e., end points occurring at the low concentrations/doses); these included respiratory, cardiovascular (myocardial and EKG alterations), gastrointestinal, metabolic (serum glucose levels), and developmental effects. Based on the level of evidence in human studies and animal studies, each health effect was categorized into one of four possible hazard identification conclusion categories: known to be a hazard to humans, presumed to be a hazard to humans, suspected to be a hazard to humans, or not classifiable as to the hazard in humans. The levels of evidence needed for each category are discussed in Appendix B. The hazard identification conclusions for antimony, resulting from the systematic review, are also presented in Appendix B and are summarized as follows:

- Antimony is presumed to cause respiratory effects following inhalation exposure based on low evidence in workers exposed to antimony oxides and a high level of evidence in several animal species exposed to antimony trioxide, antimony trisulfide, and antimony ore.

- Antimony is suspected to cause myocardial and EKG alterations based on inadequate evidence in an inhalation occupational exposure study and low evidence in inhalation and oral exposure studies in animals. This hazard identification conclusion is supported by numerous reports of cardiovascular effects in patients administered antimony compounds for the treatment of leishmaniasis and injection studies in animals.

- Antimony is presumed to cause gastrointestinal tract irritation based on inadequate evidence in human studies and high evidence in animal studies.

- Antimony is suspected to cause decreases in serum glucose levels based on high evidence from two animal oral exposure studies, supported by an animal intramuscular exposure study; human data are lacking.

- Antimony is suspected to cause developmental effects, particularly decreases in postnatal growth, based on inadequate evidence in humans and high evidence in a small number of animal studies.

3.6.2 Minimal Risk Levels (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for antimony and compounds. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

3.6.2.1 Inhalation MRLs

Acute-Duration. No human studies have evaluated the acute inhalation toxicity of antimony. In laboratory animals, the acute toxicity has been evaluated for stibine, antimony trisulfide, and antimony trioxide. These studies clearly identify the respiratory tract as one of the most sensitive targets of antimony toxicity (Brieger et al. 1954; NTP 2016; Price et al. 1979). A 30-minute exposure to 1,395 mg Sb/m^3 as stibine resulted in pulmonary edema and congestion and death in rats and guinea pigs (Price et al. 1979). Chronic lung inflammation was observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (7 hours/day) and in rats exposed to 25 mg Sb/m^3 as antimony trioxide for

12 exposures over a 16-day period (6 hours/day) (NTP 2016). NTP (2016) also found squamous metaplasia in the epiglottis of rats and mice exposed to 25 or 12 mg Sb/m^3, respectively. The primary extrarespiratory effects also observed following acute exposure were degenerative changes in the heart and altered EKGs in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide.

The Brieger et al. (1954) and NTP (2016) studies were considered for derivation of an acute-duration inhalation MRL. Although the rats and mice in the NTP (2016) study were exposed to antimony trioxide over a 16- or 17-day period, the animals were only exposed for 12 or 13 times and the study was considered to be more reflective of effects associated with acute-duration exposure than intermediate-duration exposure. Since the Brieger et al. (1954) study only tested one concentration of antimony trisulfide, the LOAEL of 19.9 mg Sb/m^3 for lung and cardiovascular effects was considered the point of departure (POD) for this study. For the NTP (2016) study, the incidence data for squamous metaplasia in rats and mice were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS) using the extra risk option. Since the response level for chronic inflammation was 0% in the controls, 3.1, 6.3, and 12 mg Sb/m^3 groups and 100% at 25 or 50 mg Sb/m^3, benchmark dose (BMD) modeling was not conducted for this end point and the NOAEL was used as the POD. A summary of the potential PODs (BMCLs for the selected models, LOAELs, or NOAELs for models without adequate fit) is presented in Table 3-9. Human equivalent concentrations (HECs) were calculated for each potential POD by adjusting for intermittent exposure (6 hours/24 hours, 5 days/7 days for NTP [2016] and 7 hours/day for Brieger et al. [1954]) and multiplying the POD_{ADJ} by the regional deposited dose ratio (RDDR) for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with the calculated average male and female terminal body weights of 0.189 and 0.281 kg for rats and mice, respectively, for the NTP (2016) study and a reference body weight of 4.0 kg for the rabbits. The POD_{HEC} values are presented in Table 3-9. The lowest POD_{HEC} was 0.035 mg Sb/m^3 for squamous metaplasia of the epiglottis in mice. This value was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) resulting in an MRL of 0.001 mg Sb/m^3.

Intermediate-Duration. Information on the toxicity of inhaled antimony following intermediate-duration exposure primarily comes from a 13-week study in rats exposed to antimony trioxide (Newton et al. 1994) that identified the respiratory tract as the most sensitive effect and 6–10-week studies in rats, rabbits, and dogs (Brieger et al. 1954) that examined a limited number of end points and identified the respiratory tract and myocardium as the most sensitive end points. The systematic review identified the

Table 3-9. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs) for Acute-Duration Inhalation MRL for Antimony

End point (reference)	PODs (mg Sb/m^3)	RDDR values[a]	HECs[b] (mg Sb/m^3)
Squamous metaplasia of the epiglottis in male and female rats (NTP 2016)	2.95 ($BMCL_{10}$)	0.162[c]	0.085
Chronic lung inflammation (NTP 2016)	12 (NOAEL)	0.545[c]	1.1
Squamous metaplasia of the epiglottis in male and female mice (NTP 2016)	0.94 ($BMCL_{10}$)	0.206[c]	0.035
Lung inflammation in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	0.203[d]	1.2
Degenerative changes in the heart and altered EKG readings in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	1.060[d]	6.2

[a]RDDR values specific for each region of the respiratory tract (extrathoracic and pulmonary) were calculated using EPA's RDDR calculator, with the average of the male and female terminal body weights of 0.189 and 0.0281 kg for rats and mice, respectively, and 4.0 kg for rabbits.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days for the NTP [2016] studies and POD x 7 hours/24 hours x 5 days/7 days for the Brieger et al. [1954] study) by the RDDR value.
[c]Calculated using a particle size of 1.4 µm (sigma g of 1.9).
[d]Calculated using a particle size of 2 µm (sigma g of 1.9); these are assumed values; the investigators noted that most of the particles were <2 µm, but did not provide any additional information.

BMCL = 95% lower confidence limit on the benchmark concentration; EKG = electrocardiogram;
EPA = Environmental Protection Agency; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level;
NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; RDDR = regional deposited dose ratio

respiratory effects as presumed health effects in humans and myocardial damage and alterations in EKGs as suspected health effect in humans. In the Newton et al. (1994) study, exposure to ≥4.11 mg Sb/m^3 resulted in increases in alveolar/intra-alveolar macrophages, increases in relative lung weights, and increases in lung clearance half-times in rats killed at the end of the exposure period. In rats allowed to recover for 27 weeks, significant increases in the incidences of chronic interstitial inflammation and fibrosis were observed in rats exposed to 19.60 mg Sb/m^3. Mild congestion and focal hemorrhages were also observed in the lungs of rats exposed to 2.20 mg Sb/m^3 as antimony trisulfide for 6 weeks (Brieger et al. 1954); however, the investigators did not report the incidence of this effect, which precludes assessing the significance of the finding. Brieger et al. (1954) also found antimony trisulfide-induced alterations in EKGs and histological alterations in the myocardium of rats exposed to 2.20 mg Sb/m^3 for 6 weeks, dogs exposed to 3.98 mg Sb/m^3 for 10 weeks (no alterations were observed in dogs exposed to 3.81 mg Sb/m^3 for 7 weeks), and rabbits exposed to 4.02 mg Sb/m^3 for 6 weeks. A third intermediate-duration study, reported unspecified lesions in the lungs, liver, kidneys, and pancreas (only qualitative data were provided), decreases in fertility, and decreases in litter size in rats exposed to 209 mg Sb/m^3 as antimony trioxide for 1.5–2 months (Belyaeva 1967).

The lung effects (increases in lung clearance time, chronic interstitial inflammation, and interstitial fibrosis) and the myocardial effects (histological alterations and altered EKGs) observed in the rats and rabbits were considered as the basis for an intermediate-duration MRL for antimony; the effects observed in dogs were not considered because reference values are not available for estimating the RDDR. BMD modeling was utilized to estimate the potential PODs for the histological alterations in the lungs observed in the Newton et al. (1994) study, but could not be utilized for the cardiac effects from the Brieger et al. (1954) studies due to the lack of incidence data. These incidence data were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option; see Appendix A for details on the BMD modeling results.

A summary of the PODs and HECs are presented in Table 3-10. The POD_{HEC} values, which were based on $BMCL_{10}$ or NOAEL values, ranged from 0.19 to 0.078 mg Sb/m^3 and the POD_{HEC} values, based on LOAEL values, were 0.89 and 1.5 mg Sb/m^3. To compare the two types of PODs, the POD_{HEC} values based on LOAELs were divided by an uncertainty factor of 10 resulting in values of 0.15 and 0.089 mg Sb/m^3. The POD_{HEC} values for the increased lung clearance half-time, chronic lung interstitial inflammation, and degenerative heart effects and altered EKG readings in rabbits were similar, and the lowest value of 0.057 mg Sb/m^3 for chronic lung inflammation was selected as the basis of the MRL.

Table 3-10. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs) for Intermediate-Duration Inhalation MRL for Antimony

End point (reference)	PODs (mg Sb/m^3)	RDDR values[a]	HECs[b] (mg Sb/m^3)
Increased lung clearance half-times in rats (Newton et al. 1994)	0.902 (NOAEL)	0.487[c]	0.078
Chronic lung interstitial inflammation in rats (Newton et al. 1994)	0.66 ($BMCL_{10}$)	0.487[c]	0.057
Chronic lung fibrosis in rats (Newton et al. 1994)	2.14 ($BMCL_{10}$)	0.487[c]	0.19
Degenerative changes in heart and altered EKG readings in rats (Brieger et al. 1954)	2.20 (LOAEL)	3.185[d]	1.5
Degenerative changes in heart and altered EKG readings in dogs (Brieger et al. 1954)	3.98 (LOAEL)	NA[e]	NA
Degenerative changes in heart and altered EKG readings in rabbits (Brieger et al. 1954)	4.02 (LOAEL)	1.060[d]	0.89

[a]RDDR values specific for each region of the respiratory tract (extrathoracic and pulmonary) were calculated using EPA's RDDR calculator, with estimated body weight of 0.230 kg for the Newton et al. (1994) study and reference body weights of 0.267 and 4.0 kg for rats and rabbits in the Brieger et al. (1954) study.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days for the Newton et al. [1994] study and 7 hours/day, 5 days/week for the Brieger et al. [1954] study) by the RDDR value.
[c]Calculated using a particle size of 3.05 µm (sigma g of 1.57).
[d]Calculated using a particle size of 2 µm (sigma g of 1.9), which is an assumed value; the investigators noted that most of the particles were <2 µm, but did not provide any additional information.
[e]RDDR calculator does not have default values for dogs and HECs could not be calculated.

BMCL = 95% lower confidence limit on the benchmark concentration; EKG = electrocardiogram; EPA = Environmental Protection Agency; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; RDDR = regional deposited dose ratio

This human equivalent value of 0.057 mg Sb/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) resulting in an MRL of 0.002 mg Sb/m^3. However, this MRL is slightly higher than the acute-duration inhalation MRL, and ATSDR adopted the acute-duration MRL of 0.001 mg Sb/m^3 for intermediate-duration exposure.

Chronic-Duration. The toxicity of airborne antimony has not been extensively studied in humans. Several occupational exposure studies have reported lung effects (pneumoconiosis and chronic bronchitis) in workers at antimony smelters (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Schnorr et al. 1995). Signs of upper respiratory tract irritation including bleeding of the nose, rhinitis, upper airway inflammation, and laryngitis (Potkonjak and Pavlovich 1983; Renes 1953) have also been reported in workers. Other effects that have been observed in workers include altered EKGs (Brieger et al. 1954) and dermatitis, which is likely due to direct contact with skin (Potkonjak and Pavlovich 1983; Renes 1953).

One study also reported reproductive disturbances and developmental effects (decreases in infant growth) in female workers exposed to metallic antimony, antimony trioxide, and antimony pentasulfide (Belyaeva 1967). Although some studies provided exposure levels, these studies were not considered suitable for derivation of chronic MRLs because many studies did not include control groups, wide ranges of antimony levels were reported, and many involved co-exposure to other compounds including arsenic.

A number of studies have evaluated the chronic toxicity of antimony compounds in rats and mice. These studies provide strong evidence that the respiratory tract is the primary target of antimony toxicity, which is supported by the systematic review of the toxicity data that concluded that respiratory tract toxicity is a presumed health effect in humans. Four studies identified LOAEL values <5 mg Sb/m^3 for lung effects in rats (Newton et al. 1994; NTP 2016; Watt 1983) and mice (NTP 2016). Watt (1983) found increases in the incidence of focal fibrosis, adenomatous hyperplasia, cholesterol clefts, and pneumocyte hyperplasia in rats exposed to 1.6 mg Sb/m^3 for 55 weeks. In rats and mice exposed to 2.5 mg Sb/m^3 as antimony trioxide for 2 years, inflammation, proteinosis, alveolar/bronchiolar hyperplasia, and fibrosis were observed in the lungs (NTP 2016). An increase in chronic lung inflammation and increased lung clearance times were observed in female rats exposed to 0.43 mg Sb/m^3 and in male and female rats exposed to 3.8 mg Sb/m^3 as antimony trioxide for 12 months; the inflammation was only observed after a 1-year recovery period (Newton et al. 1994). Higher LOAELs for lung effects were identified for other antimony compounds: 17.5 mg Sb/m^3 as antimony ore for interstitial fibrosis (Groth et al. 1986) and 84 mg Sb/m^3 as antimony trisulfide for lipoid pneumonia (Gross et al. 1952). Although these LOAELs

are higher than those identified for antimony trioxide, the available data do not allow a comparison between compounds since adverse effects were often observed at the lowest concentration tested. A summary of the NOAEL and LOAEL values identified in animal studies is presented in Table 3-11. In addition to the pulmonary effects, effects have also been observed in the lymph nodes (lymphoid hyperplasia in bronchial and mediastinal lymph nodes), eyes (lenticular degeneration), and bone marrow (hyperplasia); the LOAELs for these effects (see Table 3-11) are similar to those identified for respiratory effects.

As summarized in Table 3-11, Newton et al. (1994) identified the lowest LOAEL value for chronic interstitial lung inflammation and lenticular degeneration in rats exposed to 0.43 mg Sb/m^3 for 1 year with a 1-year recovery period; these effects were not observed at 0.05 mg Sb/m^3. The other chronic-duration studies identified higher LOAEL values.

BMD modeling was utilized to estimate the potential PODs for lung inflammation and lenticular degeneration in rats (Newton et al. 1994). The incidence data were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option. The results of the BMD modeling are presented in Appendix A. A summary of the potential PODs for each end point based on NOAEL, LOAEL, or BMCL values is presented in Table 3-12. HECs were calculated by multiplying the duration-adjusted POD by the RDDR; the RDDR was calculated for each region of the respiratory tract using EPA's RDDR calculator and the reported particle sizes. The lowest POD_{HEC} was 0.008 mg Sb/m^3 for lung inflammation in female rats. Thus, the $BMCL_{HEC}$ of 0.008 mg Sb/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) resulting in an MRL of 0.0003 mg Sb/m^3.

3.6.2.2 Oral MRLs

Acute-Duration. Studies conducted in the 1920s and 1940s demonstrate that antimony potassium tartrate is a gastrointestinal irritant in humans (Dunn 1928) and animals (as reviewed by Elinder and Friberg 1986), resulting in vomiting and diarrhea shortly after exposure. Houpt et al. (1984) demonstrated that the mean latency to vomit was 30 minutes after dogs drank 4.8 mg Sb/kg as antimony potassium tartrate. These gastrointestinal effects are likely due to the antimony concentration rather than the dose. NTP (1992) evaluated the acute toxicity of antimony potassium tartrate in 14-day drinking water studies in rats and mice. In rats, the highest concentration (61 mg Sb/kg/day) did not result in

Table 3-11. Summary of NOAEL and LOAEL Values for Effects Observed in Target Tissues Following Chronic Duration Inhalation Exposure[a]

Effect	NOAEL	LOAEL	Reference
Chronic interstitial inflammation in male rats exposed to antimony trioxide for 1 year	0.43	3.8	Newton et al. 1994
Chronic interstitial inflammation in female rats exposed to antimony trioxide for 1 year	0.05	0.43	Newton et al. 1994
Lenticular degeneration in rats exposed to antimony trioxide for 1 year	0.05	0.43	Newton et al. 1994
Lipoid pneumonia in rats exposed to antimony trisulfide for 14.5 months		84[b]	Gross et al. 1952
Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony trioxide for 1 year		36[c]	Groth et al. 1986
Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony ore for 1 year		17.5[c]	Groth et al. 1986
Focal fibrosis, pneumocyte hyperplasia in rats exposed to antimony trioxide for 55 weeks		1.6	Watt 1983
Lung inflammation, proteinosis, alveolar epithelial hyperplasia, bronchiole epithelial hyperplasia, lung fibrosis in rats exposed to antimony trioxide for 2 years		2.5	NTP 2016
Nasal respiratory epithelial hyperplasia in rats exposed to antimony trioxide for 2 years		2.5	NTP 2016
Lymphoid hyperplasia in bronchial and mediastinal lymph nodes in rats exposed to antimony trioxide for 2 years		2.5	NTP 2016
Lung inflammation, alveolar fibrosis, pleural fibrosis and inflammation, and alveolar and bronchiolar epithelial hyperplasia in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016
Nasal respiratory epithelial inflammation in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016
Bone marrow hyperplasia in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016
Lymphoid hyperplasia of bronchial lymph nodes in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016

[a]Unless otherwise noted, exposures were for 6 hours/day, 5 days/week
[b]Exposures were for 25 hours/week
[c]Exposures were for 7 hours/day, 5 days/week

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Table 3-12. Summary of Potential Points of Departure (PODs) for Derivation of Chronic-Duration Inhalation MRL for Antimony

End point (reference)	POD (mg Sb/m^3)	RDDR[a]	HEC[b] (mg Sb/m^3)
Chronic interstitial inflammation in male rats (Newton et al. 1994)	0.43 (NOAEL)	0.330	0.025
Chronic interstitial inflammation in female rats (Newton et al. 1994)	0.10 ($BMCL_{10}$)	0.436	0.0008
Lenticular degeneration in rats (Newton et al. 1994)	0.05 (NOAEL)	2.797	0.025

[a]RDDR values specific for each region of the respiratory tract (pulmonary and extrarespiratory) were calculated using EPA's RDDR calculator, with reference body weights of 0.380 and 0.229 kg for male and female rats and particle size of 3.76 µm (sigma g of 1.79).
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days) by the RDDR value.

BMCL = 95% lower confidence limit on the benchmark concentration; EPA = Environmental Protection Agency; HEC = human equivalent concentration; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; RDDR = regional deposited dose ratio

significant alterations in body weight or histopathological alterations in major tissues and organs. In mice, exposure to 150 mg Sb/kg/day resulted in focal ulceration in the forestomach and minimal to moderate hepatocellular cytoplasmic vacuolization. Exposure to 99 and 150 mg Sb/kg/day resulted in a transient decrease in body weight gain; at termination, body weights were within 93% of controls. The decreases in body weight may have been secondary to the dramatic decrease in water intake, which was also observed in the exposed mice.

Although the Houpt et al. (1984) study identified the lowest LOAEL for acute exposure, this study was not selected as the basis of the MRL because the study only evaluated overt signs of gastrointestinal irritation and was a single exposure study. The mouse study (NTP 1992) was selected as the key study for derivation of the acute-duration oral MRL. The NOAEL of 99 mg Sb/kg/day for forestomach and liver lesions was selected as the POD for the MRL. BMD modeling was not conducted since lesions were only observed in the high-dose group. The transient decrease in body weight observed at 99 and 150 mg Sb/kg/day was not selected as the POD because this decrease may have been the result of decreased water consumption likely due to taste aversion. This NOAEL of 99 mg Sb/kg/day was divided by a total uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an acute duration MRL of 1 mg Sb/kg/day.

Intermediate-Duration. Several studies have evaluated the intermediate-duration toxicity of antimony compounds. Observed effects include reductions in body weight gain, hematological effects (alterations in red blood cell and platelet levels), decreases in serum glucose levels, thyroid (epithelial alterations), and developmental effects (decreased pup body weight and altered vasomotor response in pups). The results of several 12–24-week studies provide evidence for compound-specific differences in toxicity, which are likely reflective of differences in the relative absorption of the compounds. More soluble compounds such as antimony potassium tartrate and antimony trichloride appear to be more toxic than antimony trioxide; see Table 3-13 for a list of LOAELs for different antimony compounds.

The lowest LOAEL values were identified for altered vasomotor response in pups, decreased pup growth, and decreases in serum glucose levels and these three end points were considered for the basis of the intermediate-duration MRL. Developmental toxicity and decreases in serum glucose levels were both considered suspected health effects in humans based on the systematic review of the available data on antimony; of the two developmental effects, only the decrease in growth was considered for MRL derivation due to the uncertainty associated with estimating the dose for the vasopressor studies. In these

Table 3-13. List of NOAEL and LOAEL Values in Rats Exposed to Antimony or Antimony Compounds for Intermediate Durations

Effect, duration (reference)	Compound	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)
Altered vasomotor response in pups exposed during lactation (maternal dose was 0.8 mg Sb/kg/day) and post-lactation on PNDs 22–60 (Angrisani et al. 1988)	Antimony trichloride in drinking water		0.1 (post-weaning dose)
Altered vasomotor response in pups exposed during gestation and lactation (maternal dose was 0.7 mg Sb/kg/day) and post-lactation on PNDs 22–60 (Rossi et al. 1987)	Antimony trichloride in drinking water		0.1 (post-weaning dose)
Decreased pup growth on PNDs 10–60 in pups exposed during gestation, lactation, and postnatally (Rossi et al. 1987)	Antimony trichloride in drinking water	0.07	0.7
Decreases in serum glucose in female rats exposed for 13 weeks (Poon et al. 1998)	Antimony potassium tartrate in drinking water	0.06	0.64
Decreased red blood cell count in male rats exposed for 24 weeks (Sunagawa 1981)	Antimony metal in diet		620
Cloudy swelling in hepatic cords in male rats exposed for 24 weeks (Sunagawa 1981)	Antimony metal in diet		620
Increased disorder of hepatic cords in male rats exposed for 24 weeks (Sunagawa 1981)	Antimony trioxide in diet	370	740
No alterations in hematological, serum clinical chemistry, or histopathology of major tissues and organs in rats exposed for 13 weeks (Hext et al. 1999)	Antimony trioxide in diet	1,408	

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day

studies, rats were exposed during gestation and/or lactation and then exposed on PNDs 22–60; the 0.1 mg Sb/kg/day dose is an estimate of the postnatal exposure, but does not include an estimate of prenatal exposure or exposure via breast milk. BMD modeling was considered for the decreases in serum glucose levels and decreases in pup body weight on PNDs 10 and 22. The serum glucose levels and pup body weights were fit to all available continuous models in EPA's BMDS (version 2.6.0). None of the models provided adequate fit to the serum glucose data or the PND 10 body weight data. Thus, a NOAEL/ LOAEL approach was utilized to identify the POD for the intermediate-duration oral MRL. The NOAEL and LOAEL values for the decreased serum glucose level and the decreased pup body weight were similar and the end point with the lowest LOAEL (decreased serum glucose level) was selected as the basis of the MRL. The NOAEL of 0.064 mg Sb/kg/day was divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability), resulting in an MRL of 0.0006 mg Sb/kg/day.

Chronic-Duration. Two studies have evaluated the chronic toxicity of antimony (Kanisawa and Schroeder 1969; Schroeder et al. 1970) in rats and mice exposed to antimony potassium tartrate in drinking water for a lifetime. Decreases in survival were observed in rats exposed to 0.63 mg Sb/kg/day (Schroeder et al. 1970) and in mice exposed to 0.35 mg Sb/kg/day (Kanisawa and Schroeder 1969). Both studies examined a limited number of end points. In rats, no cardiovascular or body weight alterations were observed; however, a decrease in nonfasting glucose levels was found at 0.63 mg Sb/kg/day. No hepatic or body weight alterations were observed in mice. Given the limited number of end points examined and decreases in survival at the only dose tested, neither study was considered suitable for derivation of a chronic-duration oral MRL.

3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine*

disruptors. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

No studies were located regarding endocrine disruption in humans and/or animals after exposure to antimony.

No *in vitro* studies were located regarding endocrine disruption of antimony.

3.8 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when most biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

No studies are available comparing the toxicity of antimony in adults and children. The health effects observed in adults are presumed to also occur in children. The developmental toxicity of antimony has been assessed in an inhalation study (Belyaeva 1967), an oral study (Rossi et al. 1987), and parenteral studies (Alkhawajah et al. 1996; Coelho et al. 2014a; Miranda et al. 2006). A decrease in litter size was observed in rats exposed to 209 mg Sb/m^3 as antimony trisulfide 4 hours/day for 1.5–2 months; no alterations in birth weight or pup body weights on PND 21 were found. In contrast, an oral exposure study (Rossi et al. 1987) reported no alterations in litter size in the offspring of rats exposed to 0.7 mg Sb/kg/day as antimony trichloride during gestation and lactation; however, significant decreases in pup body weight on PNDs 10–60 were found. Decreases in litter size, fetal body weight, and birth weight were observed in rats injected with meglumine antimoniate, sodium stibogluconate, or antimony trioxide

during gestation (Alkhawajah et al. 1996; Coelho et al. 2014a; Miranda et al. 2006). This study also provided evidence of transplacental transfer of antimony. Elevated antimony levels were found in fetal blood; the levels were 70% of those found in the dams (Miranda et al. 2006). However, gestation and lactational exposure to meglumine antimoniate resulted in blood antimony levels in pups that exceeded maternal blood levels (Coelho et al. 2014a).

A study by Cruz et al. (2007) compared plasma antimony levels in children (aged 2–7 years) to those of adults following intramuscular injections of 20 mg Sb/kg as meglumine antimoniate for 20 days for the treatment of leishmaniasis. The plasma antimony concentrations were significantly lower in children compared to adults and a significantly shorter elimination half-life was estimated in the children (1.48 hours) compared to the adults (1.99 hours).

3.9 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to antimony are discussed in Section 3.9.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health

impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by antimony are discussed in Section 3.9.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.11, Populations That Are Unusually Susceptible.

3.9.1 Biomarkers Used to Identify or Quantify Exposure to Antimony

Elevated blood, hair, urine, and fecal levels of antimony indicate high exposure to antimony. A significant correlation exists between the level of pentavalent antimony (N-methylglucamine antimonate) administered intraperitoneally to humans and antimony levels in hair (Dorea et al. 1989). However, Dorea et al. (1989) only tested two levels of antimony (10 and 20 mg antimony/kg/day). It should be noted that hair antimony levels have not been established as a reliable biomarker of antimony exposure. Factory workers exposed to antimony trioxide (0.042–0.70 mg antimony/m^3) had elevated urine and blood antimony levels (Ludersdorf et al. 1987). Antimony levels in the urine and blood were 1.1 and 0.9–5.0 µg/L, respectively, compared to 0.6 µg/L urine levels and 0.4 µg/L blood levels in unexposed workers. Another study of workers producing antimony pentoxide and sodium antimoniate found significant correlations between airborne antimony levels and urinary antimony levels, particularly if the air levels were compared to postshift increases in urinary levels (Bailly et al. 1991). Animal data suggest that urine and blood levels remain elevated several days after exposure (Felicetti et al. 1974b).

3.9.2 Biomarkers Used to Characterize Effects Caused by Antimony

No toxic symptoms specific to antimony exposure have been identified. Toxic effects that reportedly occur in humans include pneumoconiosis, altered EKG readings, and gastrointestinal effects. No quantitative biomarkers associated with these effects are known.

3.10 INTERACTIONS WITH OTHER CHEMICALS

No information on the influence of other compounds on the toxicity of inhaled or ingested antimony was located.

3.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to antimony than will most persons exposed to the same level of antimony in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of antimony, or compromised function of organs affected by antimony. Populations who are at greater risk due to their unusually high exposure to antimony are discussed in Section 6.7, Populations with Potentially High Exposures.

Individuals with existing chronic respiratory or cardiovascular disease or problems may have an increased risk of antimony toxicity since the respiratory and cardiovascular systems are targets of antimony toxicity. Because antimony is excreted in the urine, individuals with kidney dysfunction may be unusually susceptible.

3.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to antimony. Because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to antimony. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to antimony can be consulted for medical advice. The following texts provide specific information about treatment following exposures to antimony:

Tarabar AF. 2015. Antimony. In: Goldfrank's toxiologic emergencies, 10th Edition. New York, NY. McGraw Hill, 1161-1167.

Schonwald S. 2004. Antimony. In: Dart, RC, ed. Medical toxicology, 3rd Edition. Philadelphia, PA: Lippincott Williams & Wilkins, 1391-1392.

Shannon MW, Borron SW, Burns MJ. 2007. Antimony. In: Haddad and Winchester's clinical management of poisoning and drug overdose. Philadelphia, PA: Saunders Elsevier, 917, 1158.

These texts are provided solely for informational purposes and are not intended as a substitute for consultation with a medical professional.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

3.12.1 Reducing Peak Absorption Following Exposure

Human exposure to antimony may occur by inhalation, ingestion, or dermal contact. Mitigation approaches to reduce absorption of antimony have included general recommendations of removal from the exposure and removal of contaminated clothing from the exposed individual. For ingestion, gastric lavage may be beneficial (Tarabar 2014). Exposed eyes and skin should be flushed with a clean neutral solution such as water or normal saline.

3.12.2 Reducing Body Burden

Antimony may be found in the blood and urine several days after exposure. Pentavalent antimony is rapidly excreted in humans following intravenous or intramuscular administration, with >50% excreted in the urine 6 hours after injection (Goodwin and Page 1943; Rees et al. 1980). Trivalent antimony is not as rapidly excreted in the urine and is primarily excreted in the feces over a 24-hour period of time as noted after intraperitoneal administration in laboratory animals (Edel et al. 1983).

Little data are available on reducing the antimony body burden. The effectiveness of chelation therapy has been tested in laboratory animals (Eagle et al. 1947). Administration of dimercaprol (also referred to as British anti-Lewisite or BAL) decreased the mortality associated with intravenous administration of fuadin or tartar emetic in rabbits. Dimercaprol was also used as a treatment in four individuals ingesting food contaminated with tartar emetic (Lauwers et al. 1990). Administration of dimercaprol resulted in increases in urinary excretion of antimony. In a study in mice administered lethal doses of potassium antimony tartrate, administration of dimercaptosuccinic acid was the most effective in decreasing the mortality incidence, as compared to Tiron, sodium 2,3-dimercaptopropane, and D-penicillamine (Basinger et al. 1981). Other chelating agents tested, including dimercaprol, tartaric acid,

ethylenediaminetetraacetic acid (EDTA), and sodium diethledithiocarbamate, were not effective in increasing survival; it is noted that dimercaprol was administered at a low dose due to toxicity.

3.12.3 Interfering with the Mechanism of Action for Toxic Effects

No information on interfering with the mechanism of action was identified.

3.13 ADEQUACY OF THE DATABASE

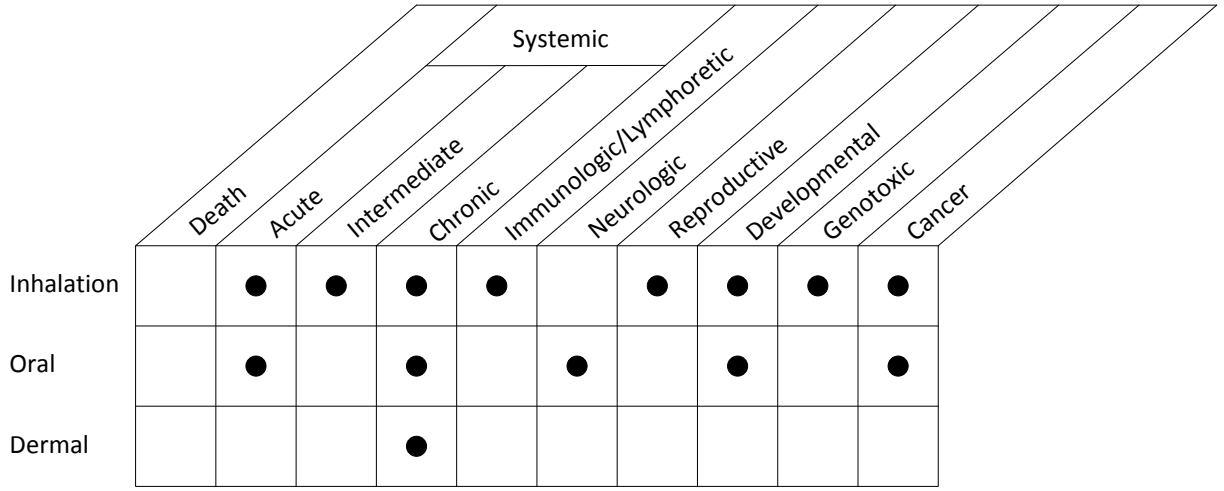
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of antimony is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of antimony.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

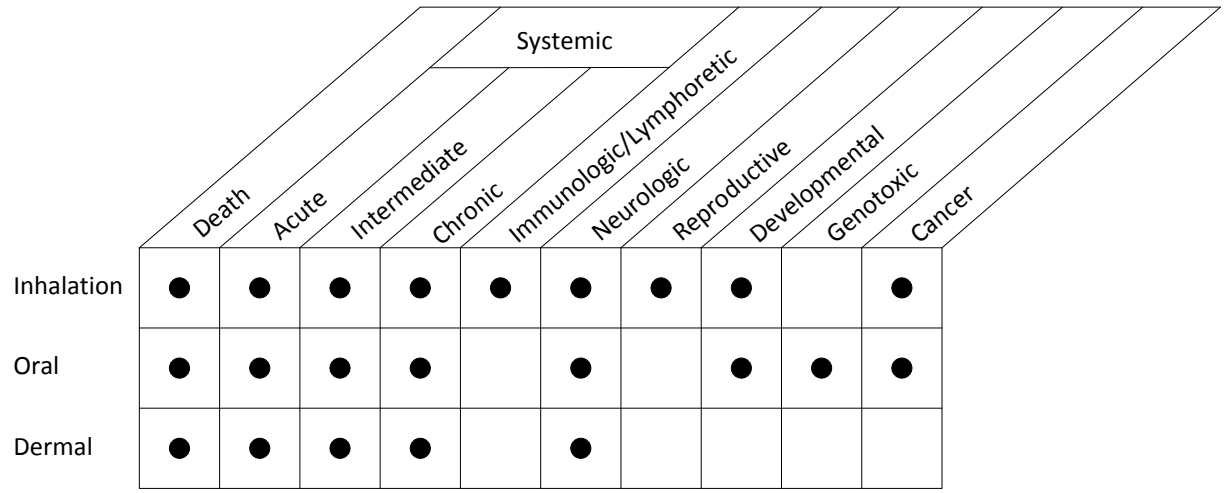
3.13.1 Existing Information on Health Effects of Antimony

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to antimony are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of antimony. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-4. Existing Information on Health Effects of Antimony



Human



Animal

● Existing Studies

As seen in Figure 3-4, there are data available on the health effects of antimony in humans following inhalation, oral, or dermal exposure. The inhalation data consist of several reports of workers exposed to inorganic forms of antimony. However, most of these studies are incomplete because the workers were exposed to a variety of compounds or the exposure level was not reported. One oral study involving accidental drinking of lemonade contaminated with potassium antimony tartrate was located. Other studies are population-based studies examining the relationship between urinary antimony levels and health effects. The dermal data on humans are limited to a study in which antimony was applied to the skin of volunteers and occupational exposure studies involving dermal exposure to airborne antimony.

As compared to the human data, more complete information on the systemic health effects of antimony in animals was located. Inhalation studies predominantly evaluated the systemic toxicity of antimony trioxide, although some studies were available for antimony trisulfide and antimony ore. One inhalation study evaluated the reproductive and developmental toxicity of antimony. Several studies that examined the toxicity of metallic antimony, antimony trioxide, antimony trichloride, and potassium antimony tartrate via oral exposure were located. Sensitive measurements of cardiovascular toxicity were not examined in most of these studies. One developmental toxicity study in rats was located; internal examination of pups was not performed. The acute and intermediate toxicity of dermally applied antimony trioxide, antimony oxide, and antimony thioantimonate has been examined. However, the available studies did not examine the systemic toxicity of antimony; they were designed to assess the dermal and/or ocular toxicity of antimony.

3.13.2 Identification of Data Needs

Acute-Duration Exposure. Information on the target organs of acute exposure in humans to antimony is limited. Based on one human study, the gastrointestinal tract appears to be a target following inhalation exposure to antimony (Taylor 1966). Animal studies have shown that the respiratory tract and heart are the primary targets following inhalation exposure to antimony (Brieger et al. 1954; NTP 2016; Price et al. 1979); there are also limited data suggesting that the liver and kidney are also targets of antimony toxicity (Brieger et al. 1954). An acute inhalation MRL based on respiratory effects in mice (NTP 2016) was derived. The gastrointestinal tract appears to be a target in humans and animals following oral exposure to antimony. This is based on a report of workers who accidentally drank lemonade contaminated with antimony potassium tartrate (Dunn 1928), a dog study reporting vomiting after ingestion of antimony potassium tartrate (Houpt et al. 1984), and a mouse study reporting forestomach ulceration (NTP 1992). Results of the mouse study also suggest that the liver may be a

target of antimony toxicity. An acute oral MRL based on the forestomach and liver effects observed in mice was derived. There is no information on the target organs in humans following dermal exposure to antimony. Application of antimony to the skin or eyes of animals results in mild irritation (Gross et al. 1955; Horton et al. 1986; Myers et al. 1978); eye irritation was also observed when animals were exposed to airborne antimony compounds (Price et al. 1979). Information about the toxicity of different antimony compounds, as well as differences in valence states, was not located. Additional acute-duration studies by the inhalation, oral, and dermal routes would provide information on differences in the potency of various antimony compounds.

Intermediate-Duration Exposure. No reports of health effects in humans following intermediate-duration inhalation, oral, or dermal exposure were located. Animal data suggest that the heart and respiratory tract are the likely targets of antimony toxicity following inhalation exposure (Brieger et al. 1954; Newton et al. 1994). Developmental and reproductive effects have also been reported in animals (Belyaeva 1967). There is no information on human health effects following intermediate-duration oral exposure to antimony. The database was adequate for derivation of an intermediate-duration inhalation MRL; however, the resulting value was slightly higher than the acute-duration MRL and the acute MRL was adopted for an intermediate-duration MRL. Several studies in rats have evaluated the toxicity of antimony following oral exposure (Angrisani et al. 1988; Hext et al. 1999; Poon et al. 1998; Rossi et al. 1987; Sunagawa 1981). These studies have investigated the toxicity of several trivalent antimony compounds (antimony trichloride, antimony potassium tartrate, and antimony trioxide) and metallic antimony and found differences in effect levels that may be related to solubility and absorption efficiency. The most sensitive effects were decreases in blood glucose levels, alterations in red blood cell counts, hepatic alterations, and developmental toxicity. Although the database was considered adequate for derivation of an intermediate-duration oral MRL, additional studies examining EKGs would increase the confidence in this MRL, since myocardial damage is a suspected human health effect but has not been adequately assessed in oral exposure studies. An intermediate-duration dermal exposure study did not report significant alterations in the liver, kidney, skin, or EKGs (Horton et a. 1986). An intermediate-duration study reported corneal opacities in rats exposed to airborne antimony trioxide (Newton et al. 1994). Additional dermal exposure studies could provide useful information on the dermal toxicity of different antimony compounds.

Chronic-Duration Exposure and Cancer. There are several human studies that indicate that the targets appear to be the respiratory tract, heart, and skin following chronic-duration exposure (Brieger et al. 1954; Cooper et al. 1968; Potkonjak and Pavlovich 1983). Animal studies provide strong evidence

that the respiratory tract is the primary target of antimony toxicity (Gross et al. 1952; Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983). Most of the studies tested antimony toxicity, and studies evaluating antimony ore (Groth et al. 1986) or antimony trisulfide (Gross et al. 1952) reported lung effects at the lowest concentration tested; therefore, they are not useful for comparing the relative toxicity of various antimony compounds. Chronic animal studies were considered adequate for deriving a chronic-duration inhalation MRL. Several epidemiology studies have evaluated the potential toxicity of environmental exposure to antimony using urinary antimony levels as a biometric (Mendy et al. 2012; Shiue 2014, 2015; Shiue and Hristova 2014); these studies are not adequate for establishing causality. Data on chronic oral toxicity are limited to two studies involving lifetime exposure to antimony potassium tartrate (Kanisawa and Schroeder 1969; Schroeder et al. 1970). Both studies only tested one concentration and examined a limited number of end points; since decreases in survival were observed in both studies, they were not considered suitable for derivation of a chronic-duration oral MRL. Well-designed oral experiments, using several exposure levels and measuring all sensitive toxicological end points, would provide information on the health effects associated with long-term exposure to antimony.

Two occupational exposure studies have found increases in the risk of lung cancer in workers (Jones 1994; Schnorr et al. 1995); the carcinogenicity of antimony in humans following oral or dermal exposure has not been investigated. Evidence for the carcinogenicity of inhaled antimony in animals is mixed. Two 1-year studies reported lung tumors in rats exposed to relatively low levels of antimony trioxide (Groth et al. 1986; Watt 1983). A study using similar exposure levels and exposure durations did not find evidence of carcinogenicity (Newton et al. 1994). On the other hand, a 2-year study concluded that there was some evidence of carcinogenic activity in male and female rats and clear evidence of carcinogenic activity in male and female mice (NTP 2016). The oral cancer data in animals are limited to studies that used very low levels of antimony (Kanisawa and Schroeder 1969; Schroeder et al. 1970). No dermal cancer studies in animals were located; however, an inhalation study found an increase in squamous cell carcinoma of the skin, which may have been related to exposure to antimony trioxide (NTP 2016). Oral and dermal studies in rodents using several exposure levels including the maximum tolerated level would provide useful information because prolonged exposure to antimony in humans may occur.

Genotoxicity. *In vivo* studies have evaluated the potential of trivalent and pentavalent antimony compounds to induce clastogenic effects and damage DNA in humans (Cavallo et al. 2002; Hantson et al. 1996), rats (Kirkland et al. 2007), and mice (Elliott et al. 1998; Gurnani et al. 1992a, 1992b; Lima et al. 2010). *In vitro* studies have examined the potential of metallic antimony, antimony trioxide, antimony trichloride, antimony pentachloride, antimony pentoxide, and antimony potassium tartrate to induce gene

mutations (Asakura et al. 2009; Elliott et al. 1998; Kubo et al. 2002; Kuroda et al. 1991; Lantzsch and Gebel 1997; Zeiger et al. 1992) or DNA damage (Kanematsu et al. 1980; Kuroda et al. 1991) in bacteria. *In vitro* studies have also evaluated the potential of a variety of trivalent and pentavalent antimony compounds to induce clastogenic damage, gene mutations, or DNA damage in mammalian cells (Asakura et al. 2009; Elliott et al. 1998; Gebel et al. 1998a; Huang et al. 1998; Kuroda et al. 1991; Lima et al. 2010; Migliore et al. 1999; Paton and Allison 1972; Schaumlöffel and Gebel 1998; Tu and Sivak 1984). No additional studies of genotoxicity are suggested at this time.

Reproductive Toxicity. Women exposed to antimony in the workplace have reported menstrual disturbances and a higher incidence of spontaneous abortions compared with nonexposed workers (Belyaeva 1967). From this report, it is unclear what the exposure level was, whether the women were exposed also to other compounds, and whether the controls had comparable jobs. Reproductive effects (failure to conceive, uterine metaplasia) have been observed in rats exposed to airborne antimony (Belyaeva 1967). Data on the reproductive toxicity of antimony following oral exposure are limited to a series of studies evaluating sperm parameters in rats and mice exposed to antimony trioxide or antimony potassium tartrate (Omura et al. 2002). Well-designed studies to assess the effects of inhalation or orally administered antimony on reproductive performance would provide information on possible reproductive effects that might be relevant to humans.

Developmental Toxicity. An increased number of spontaneous abortions was observed in women exposed to antimony in the workplace (Belyaeva 1967). However, there are several limitations to this study, as discussed above in the reproductive toxicity section. No overt developmental effects were observed in the offspring of these women. Two other epidemiology studies did not find associations between antimony levels in drinking water and the prevalence of neural tube defects (Longerich et al. 1991) and or between umbilical cord antimony levels and adverse pregnancy outcomes (Zheng et al. 2014). A developmental toxicity study in rats found decreases in pup growth and no alterations in the occurrence of structural abnormalities resulting from gestational exposure to antimony potassium tartrate in drinking water (Rossi et al. 1987). Additionally, two studies examining the effect of antimony on the development of the cardiovascular system found alterations in vasomotor reactivity in the offspring (Angrisani et al. 1988; Rossi et al. 1987); however, since this end point was not examined in adults, it is difficult to determine whether the effects are developmental in nature. Additional studies examining the potential of antimony to affect the development of the cardiovascular system would be useful.

Immunotoxicity. There is limited information on the immunotoxicity of antimony. A human study found alterations in immunoglobin levels (Kim et al. 1999). Inhalation studies have reported hyperplasia in the bronchial and mediastinal lymph nodes following chronic exposure in rats and mice (Newton et al. 1994; NTP 2016). An oral study found histological alterations in rats exposed to antimony potassium tartrate (Poon et al. 1998). A skin sensitization study concluded that dermal exposure to antimony thioantimonate did not result in sensitization (Horton et al. 1986). Additional studies are needed to evaluate whether antimony alters immune function.

Neurotoxicity. The potential neurotoxicity of antimony has not been investigated in humans or animals following inhalation, oral, or dermal exposure. An occupational exposure study (Renes 1953) reported some neurological effects; however, the lack of a control group and co-exposure to other compounds including arsenic limits establishing causality with antimony. Animal studies have not found histological alterations in the brain following inhalation or oral exposure (Groth et al. 1986; Hext et al. 1999; NTP 1992, 2016; Poon et al. 1998; Watt 1983). A study in which mice were repeatedly administered antimony potassium tartrate via intraperitoneal injections reported degenerative changes in the anterior horn cells of the lumbar spine and sciatic nerve edema (Mansour and Reese 1965). Although this effect has not been observed by other routes of exposure, this end point has not been well studied. Sensitive tests of neurophysiological function may detect early signs of neurotoxicity following inhalation, oral, or dermal exposure to antimony.

Epidemiological and Human Dosimetry Studies. There are several epidemiological occupational exposure studies (Belyaeva 1967; Brieger et al. 1954; Cooper et al. 1968; Jones 1994; Kim et al. 1999; Potkonjak and Pavlovich 1983; Renes 1953; Schnorr et al. 1995; Stevenson 1965). However, most of these studies are incomplete because the exposure level and/or particle size of the airborne antimony was not reported, many studies did not include control groups, and/or the workers were often exposed to a variety of other compounds. Several studies have used NHANES data sets to examine associations between urinary antimony levels and health effects (Mendy et al. 2013; Shiue 2014, 2015; Shiue and Hristova 2014); these studies are not suitable for establishing causality. Epidemiological studies would be useful in order to determine the effects of long-term exposure in humans, with particular attention paid to cardiovascular and respiratory effects. If a cause/effect relationship was established between antimony exposure and health effects in humans, monitoring of individuals living near hazardous waste sites could be performed in order to verify that exposure levels do not exceed recommended limits and that body tissue and fluid levels remain below potentially hazardous levels.

Biomarkers of Exposure and Effect.

Exposure. Antimony levels can be measured in blood, urine, feces, and hair, and background urinary levels of antimony have been established in the general U.S. population (CDC 2015). Antimony levels in blood, urine, and feces have been shown to increase in response to increased antimony exposure (Cooper et al. 1968; Edel et al. 1983; Felicetti et al. 1974a, 1974b; Gerber et al. 1982; Goodwin and Page 1943; Ludersdorf et al. 1987; Rees et al. 1980). Studies that quantified the relationship between blood and/or urinary levels and airborne antimony concentrations or antimony intake would provide valuable information for screening.

Effect. No antimony-specific biomarkers of effects have been identified. Future studies on the toxicity of antimony should use several antimony exposure levels; this may lead to the identification of subtle biochemical or physiological biomarkers of effects.

Absorption, Distribution, Metabolism, and Excretion. There is some information on the toxicokinetic properties of antimony following oral or inhalation exposure in humans and animals (Ainsworth et al. 1991; Cooper et al. 1968; Edel et al. 1983; Felicetti et al. 1974a, 1974b; Gerber et al. 1982; Gerhardsson et al. 1982; Goodwin and Page 1943; Kirkland et al. 2007; Kobayashi and Ogra 2009; Ludersdorf et al. 1987; Newton et al. 1994; Rees et al. 1980; Ribiero et al. 2010; Sumino et al. 1975; Sunagawa 1981; Thomas et al. 1973; Yu and Rappaport 1996). However, there is limited comparative information on the absorption, distribution, and excretion of different antimony compounds. Furthermore, the site and mechanism of antimony absorption from the gastrointestinal tract have not been elucidated. The influence of nutritional factors as well as the presence of food in the gastrointestinal tract on absorption are not known. Information on the absorption, distribution, and excretion of antimony following dermal application is not known. In addition, a study on the effect of oxidation state on the cellular uptake of antimony and the effect of water solubility of an antimony compound on lung retention/ absorption would provide useful information on the toxicity of different antimony compounds. A study that examined these aspects of antimony would be useful in assessing the potential target organs following dermal exposure to antimony.

Comparative Toxicokinetics. Species differences in the toxicokinetics of antimony have been identified (Ainsworth et al. 1990; Felicetti et al. 1974a; Gross et al. 1955; Thomas et al. 1973). However, the absorption, distribution, and excretion of antimony following oral or inhalation exposure in humans is

not known. Thus, it is not possible to determine which animal species is the best model for assessing the toxicity of antimony. Information on the toxicokinetic properties of antimony in humans would be useful.

Methods for Reducing Toxic Effects. There is limited information on reducing the toxic effects of antimony. Laboratory animal studies have evaluated the effectiveness of several chelating agents in decreasing the lethality of injected antimony compounds (Basinger et al. 1981; Eagle et al. 1947). However, there are limited data on the effectiveness of these treatments in humans. Studies examining the effectiveness of chelating agents and possible side effects would be helpful in determining the most effective treatment for antimony toxicity. Antimony is widely distributed throughout the body. The hair and skin contain the highest levels of antimony. The adrenal glands, lung, large intestine, trachea, cerebellum, and kidneys also contain relatively high levels of antimony (Muramatsu and Parr 1988; Sumino et al. 1975). No information on methods of mitigating the toxicity of antimony were located. Studies that examined such methods would be useful in the treatment of antimony toxicity.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

No studies have examined the potential differences in antimony toxicity between adults and children. A toxicokinetic study comparing the distribution and elimination of intramuscularly administered pentavalent antimony found differences in serum antimony levels and elimination half-times between children and adults (Cruz et al. 2007). Toxicity and toxicokinetic studies involving inhalation and oral exposure to mature and young animals would provide valuable information for determining whether children are more susceptible to antimony toxicity.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.13.3 Ongoing Studies

No ongoing studies examining the toxicity or toxicokinetics of antimony were identified in the National Institute of Health (NIH) RePORTER (2015) database.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Antimony (Sb) is in the fourth row of group 5A (IUPAC group 15) in the periodic table, residing between arsenic and bismuth. Antimony displays four oxidation states: -3, 0, +3, and +5. The most common and stable oxidation states of antimony in aqueous solutions and biological fluids are Sb(III) and Sb(V). Antimony is sometimes referred to as a metalloid, indicating that it displays both metallic and nonmetallic characteristics (Li 2011).

Table 4-1 lists the common synonyms, trade names, and other pertinent identification information for antimony and selected antimony compounds.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of antimony and selected antimony compounds are given in Table 4-2. Antimony metal is stable under ordinary conditions. Antimony is a poor conductor of heat and electricity (Li 2011). Antimony forms complex ions with organic and inorganic acids. Stable complexes, such as $Sb_2S_4^{2-}$, may form when antimony is in the presence of sulfur (Bodek et al. 1988).

Stibine (SbH_3) is a gaseous antimony compound in which antimony is in the -3 valence state. Stibine is formed by the action of acids on metal antimonides or antimony alloys by the reduction of antimony compounds, or by the electrolysis of acidic or basic solutions where antimony is present in the cathode. There is a danger of stibine being liberated from overcharged lead storage batteries in which antimony is alloyed into the lead. Stibine slowly decomposes into metallic antimony and hydrogen. It is readily, and sometimes violently, oxidized by air to form antimony trioxide and water (Freedman et al. 1978).

Table 4-1. Chemical Identity of Antimony and Compounds[a]

Characteristic	Information		
Chemical name	Antimony	Antimony pentasulfide	Antimony pentoxide
Synonym(s)	Antimony black; stibium, antimony regulus	Antimonial saffron; antimonic sulfide; antimony red; antimony; golden antimony sulfide, antimony persulfide[c]	Antimonic oxide; antimony pentaoxide; diantimony pentoxide; stibic anhydride; antimonic anhydride; antimonic acid[c]
Registered trade name(s)	No data	No data	No data
Chemical formula	Sb[b]	S_5Sb_2[d]	O_5Sb_2[d]
Chemical structure	Sb	No data	No data
Identification numbers:			
CAS registry	7440-36-0	1315-04-4	1314-60-9
NIOSH RTECS	CC4025000	CC6125000[c]	CC6300000[c]
EPA hazardous waste	No data	No data	No data
OHM/TADS	7216595	No data	No data
DOT/UN/NA/IMDG shipping	UN 2871	No data	No data
HSDB	508	No data	No data
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Antimony and Compounds[a]

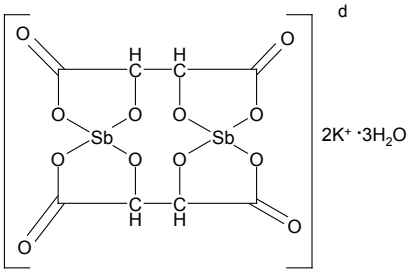
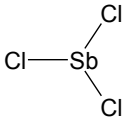
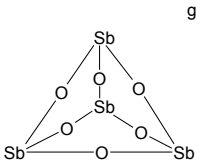
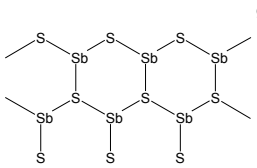
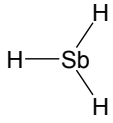
Characteristic	Information	
Chemical name	Ammonium potassium tartrate	Antimony trichloride
Synonym(s)	Antimonial potassium tartrate; potassium antimonial tartrate; tartox; tartrated antimony; potassium antimony tartrate; tartar emetic	Antimonous chloride; antimony butter; antimony(III) chloride; trichlorostibine; chloride antimony
Registered trade name(s)	No data	No data
Chemical formula	$C_8H_4K_2O_{12}Sb_2 \cdot 3H_2O$[d]	Cl_3Sb
Chemical structure		
Identification numbers:		
CAS registry	28300-74-5	10025-91-9
NIOSH RTECS	CC6825000	CC4900000
EPA hazardous waste	No data	No data
OHM/TADS	7217219	7217220
DOT/UN/NA/IMDG shipping	UN 1551	UN 1733
HSDB	1428	439
NCI	No data	No data

Table 4-1. Chemical Identity of Antimony and Compounds[a]

Characteristic	Information		
Chemical name	Antimony trioxide	Antimony trisulfide	Stibine
Synonym(s)	Antimonious oxide; antimony oxide; diantimony trioxide[d]; flowers of antimony[d]; antimony sesquioxide[e]; senmarmontite; valentinite; antimony white; antimony peroxide; timothox; exitelite	Antimonous sulfide; antimony glance; antimony orange; antimony crimson; antimony sesquisulfide; antimony sulfide; antimony vermilion; stibite; antimony needles	Antimony hydride; antimony trihydride; hydrogen antimonide
Registered trade name(s)	Hd[f]; LP[f]; KR[f]; White Star[f]; White Star M[f]; KR-LTS[f]; Thermoguard S[f]; Thermoguard L[f]; H Grade[f]; L Grade[f]; Fire Shield L[f]; Montana Brand[f]	No data	No data
Chemical formula	O_3Sb_2	S_3Sb_2	H_3Sb
Chemical structure	 [g]	 [g]	
Identification numbers:			
CAS registry	1309-64-4	1345-04-6	7803-52-3
NIOSH RTECS	CC5650000	CC9450000	WJ0700000
EPA hazardous waste	No data	No data	No data
OHM/TADS	7217222	No data	No data
DOT/UN/NA/IMDG shipping	UN 1549 antimony compounds, inorganic solid, NOS; NA 9201 antimony trioxide	UN 1549 antimony compounds, inorganic solids, NA 1325 antimony sulfide, solid	UN 2676
HSDB	436	1604	785
NCI	C55152	No data	No data

[a]All information obtained from HSDB (2005a, 2005b, 2009a, 2009b, 2013, 2014) except where noted.
[b]Weast 1988
[c]RTECS 2015
[d]Windholz 1983
[e]Freedman et al. 1978
[f]Avento and Touval 1980
[g]Cotton and Wilkinson 1966

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of Antimony and Compounds[a]

Property	Information		
Chemical name	Antimony	Antimony pentasulfide	Antimony pentoxide
Molecular weight	121.75	403.80	323.5 (anhydrous)
Color	Silvery white	Yellow	Yellow
Physical state	Solid	Solid	Solid
Valence state	0	+5	+5
Melting point (°C)	630.5	75 (decomposes)	380 (decomposes)[f]
Boiling point (°C)	1,750; 1,325[b]; 1,635[c]	No data	No data
Density (g/cm^3) at 20°C	6.684 (at 25°C); 6.688[b]	4.12	3.78
Odor	No data	Odorless[c]	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility:			
Water at 20°C	Insoluble	Insoluble	Very slightly soluble
Organic solvents	No data	Insoluble	No data
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure (mmHg) at 20°C	1 (at 886°C)[d]	No data	No data
Henry's law constant at 25°C	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors (ppm to mg/m^3)	None[e]	None[e]	None[e]
Explosive limits	No data	No data	No data

Table 4-2. Physical and Chemical Properties of Antimony and Compounds[a]

Property	Information	
Chemical name	Antimony potassium tartrate	Antimony trichloride
Molecular weight	333.93	228.11
Color	Colorless	Colorless
Physical state	Solid	Solid
Valence state	+3	+3
Melting point (°C)	100 (-½ mole H_2O)	73.4
Boiling point (°C)	No data	283, 222.6[g]
Density (g/cm^3) at 20°C	2.6	3.140 (at 25°C)
Odor	Odorless[g]	Sharp, unpleasant
Odor threshold:		
Water	No data	No data
Air	No data	No data
Taste	Sweetish, metallic[c]	No data
Taste threshold	No data	No data
Solubility		
Water at 20°C	83 g/L (cold)	6,016 g/L (at 0°C)
Organic solvents	Insoluble in alcohol; soluble in glycerine	Soluble in ABS alcohol, tartaric acid, methylene chloride, benzene, acetone
Partition coefficients		
Log K_{ow}	No data	No data
Log K_{oc}	No data	No data
Vapor pressure (mmHg) at 20°C	No data	1 (at 49.2°C, sublimes)
Henry's law constant at 25°C	No data	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits	No data	No data
Conversion factors (ppm to mg/m^3)	None[e]	None[e]
Explosive limits	No data	No data

Table 4-2. Physical and Chemical Properties of Antimony and Compounds[a]

Property	Information		
Chemical name	Antimony trioxide	Antimony trisulfide	Stibine
Molecular weight	291.50	339.69	124.77
Color	White (senarmontite); colorless (valentinite)	Black (stibinite); yellow-red (amorphous)	Colorless[g]
Physical state	Solid	Solid	Gas
Valence state	+3	+3	-3
Melting point (°C)	656	550	-88
Boiling point (°C)	1,550 (sublimes); 1,425[g]	1,150	-17[g]
Density (g/cm^3) at 20°C	5.2 (senarmontite); 5.67 (valentinite)	4.64 (stibinite); 4.12 (amorphous solid)	2.204 (at -17°C)
Odor	Odorless	No data	Disagreeable, like hydrogen sulfide[g]
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Taste	No data	No data	No data
Taste threshold	No data	No data	No data
Solubility			
Water at 20°C	Very slightly soluble	1.75 mg/L (at 18°C)	4.1 g/L (at 0°C)
Organic solvents	Soluble in tartaric acid, acetic acid, hydrochloric acid	Soluble in alcohol; insoluble in acetic acid	Soluble in carbon disulfide, ethanol[g]
Partition coefficients			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure (mmHg) at 20°C	1 (at 574°C)[d]	No data	No data
Henry's law constant at 25°C	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	No data	No data
Conversion factors (ppm to mg/m^3)	None[e]	None[e]	1 ppm stibine = 5.1 mg/m^3
Explosive limits	No data	No data	No data

[a]All information obtained from Weast (1988) except where noted.
[b]Herbst et al. 1985
[c]Windholz 1983
[d]HSDB 2013
[e]Since these substances exist in the atmosphere in the particulate state, the concentration is expressed as mg/m^3.
[f]Lewis 2012
[g]Freedman et al. 1978

This page is intentionally blank.

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

Tables 5-1 and 5-2 list the number of facilities in each state that have produced, imported, processed, or used antimony and its compounds, according to reports made to the EPA under requirements of Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 and subsequently published in the Toxic Chemical Release Inventory (TRI14 2016). Only certain types of facilities were required to report; therefore, this is not an exhaustive list. The number of individual facilities and the amount produced on site varied in each state.

Fifteen countries mine antimony. The world total mine production was 118,000 metric tons in 2000 (USGS 2004). The majority, 85% of the world total, of antimony is mined in China. Between 1977 and 1984, the amount of antimony mined in the United States ranged from 311 to 760 metric tons (Llewellyn 1989; Plunkert 1982). The United States no longer mines antimony. The last domestic mine in the United States closed in 2001. According to the U.S. Bureau of Mines, six companies produced primary antimony metal and metal oxide products in the United States in 1992. These six companies were ASARCO Incorporated, Omaha, Nebraska; Amspec Chemical Corp., Gloucester City, New Jersey; Anzon America, Laredo, Texas; Laurel Industries Inc., La Porte, Texas; Sunshine Mining Co., Kellogg, Idaho; and U.S. Antimony Corp, Thompson Falls, Montana (HSDB 2005a).

In 1992, the total U.S. primary antimony consumption was 12,221 metric tons, of which 3,297 metric tons were for metal products, 2,103 metric tons for nonmetal products, and 6,821 metric tons for flame retardants (USGS 2004). Most of the primary antimony generated in the United States was generated as antimony trioxide. Antimony trioxide is produced by oxidizing antimony sulfide ore or antimony metal in air at 600–800°C (Avento and Touval 1980). In 1987 and 1988, 18,758, and 18,226 metric tons of the oxide were produced, respectively (U.S. Bureau of Mines 1989). Consumption trends have generally paralleled those of production.

Antimony is also produced as a byproduct of smelting primary lead ores. Primary smelter outputs were 19,675 metric tons in 1992. Almost as much antimony is produced from scrap as from ore. Antimony produced from secondary sources is primarily derived from "old scrap," generally consisting of lead battery plates, type metal, and bearing metal. "New scrap," which is derived from drosses and scrap generated during fabrication, constituted 6% of the secondary antimony in 1992 (HSDB 2005a; Llewellyn 1989). Secondary antimony is chiefly consumed as antimonial lead; a small percentage goes into the

Table 5-1. Facilities that Produce, Process, or Use Antimony

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	4	1,000	999,999	1, 5, 7, 8
AR	2	100	99,999	7, 8
AZ	1	0	99	11
CA	4	0	999,999	2, 3, 7, 9, 12, 14
CT	1	1,000	9,999	7
FL	1	0	99	1, 5
IA	2	1,000	99,999	8
ID	3	1,000	999,999	8, 9, 12
IL	1	10,000	99,999	8, 11
IN	3	1,000	99,999	1, 5, 8, 9, 12, 14
KS	2	10,000	99,999	1, 4, 7, 8
KY	2	10,000	99,999	2, 3, 4, 6, 7, 8, 9
MI	2	10,000	99,999	7
MN	3	1,000	999,999	7, 8, 12
MO	4	0	99,999	1, 6, 7, 8, 9, 12, 13
MS	3	10,000	99,999	8
MT	1	100,000	999,999	1, 2, 3, 4, 5, 7
NC	4	1,000	99,999	7, 8, 14
NE	3	1,000	99,999	7, 8
NH	1	0	0	0
NJ	2	10,000	999,999	2, 4, 9, 11
NV	2	10,000	99,999	8, 12
NY	2	1,000	9,999	8
OH	12	100	999,999	1, 2, 3, 7, 8, 9, 10, 11
OR	1	10,000	99,999	12
PA	6	1,000	999,999	7, 8, 10, 14
SC	1	100,000	999,999	7, 14
TN	3	1,000	99,999	1, 4, 7, 8
TX	5	0	99,999	1, 5, 8, 9, 12
VA	3	1,000	99,999	2, 3, 7, 8
WA	2	1,000	99,999	7, 8, 11
WI	2	1,000	9,999	8

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI14 2016 (Data are from 2014)

Table 5-2. Facilities that Produce, Process, or Use Antimony Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	1	10,000	99,999	1, 5, 12, 13, 14
AL	8	1,000	99,999	2, 3, 7, 8, 10, 11, 12
AR	3	1,000	99,999	8, 9, 12
AZ	3	10,000	999,999	1, 2, 5, 8, 13, 14
CA	15	1,000	999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 12
CO	2	100,000	999,999	1, 2, 3, 4, 6, 13
CT	4	10,000	999,999	7, 8
DE	1	100,000	999,999	1, 2, 3, 7, 8, 14
FL	2	10,000	999,999	2, 3, 7, 8
GA	22	100	999,999	1, 2, 3, 5, 6, 7, 8, 14
IA	2	1,000	99,999	7, 8
ID	3	10,000	99,999	1, 5, 7, 13, 14
IL	21	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14
IN	27	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 12, 13, 14
KS	8	1,000	999,999	1, 3, 6, 7, 8
KY	19	100	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
LA	9	0	999,999	1, 3, 5, 7, 10, 11, 12
MA	17	1,000	999,999	1, 2, 3, 4, 6, 7, 8, 9
MD	1	0	0	0
MI	9	1,000	99,999	1, 2, 3, 4, 5, 7, 8, 9, 14
MN	10	1,000	999,999	7, 8, 9, 11, 12
MO	10	1,000	9,999,999	1, 2, 3, 4, 7, 8, 12
MS	11	1,000	9,999,999	6, 7, 8, 12
MT	2	100,000	999,999	1, 5, 12, 14
NC	20	1,000	99,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 14
ND	1	100,000	999,999	1, 5, 12, 13, 14
NE	5	1,000	99,999	6, 7, 8, 12
NH	2	1,000	99,999	7, 8
NJ	10	1,000	999,999	2, 3, 7, 8, 10
NV	8	0	9,999,999	1, 2, 5, 7, 12, 13, 14
NY	6	1,000	99,999	1, 7, 8, 12, 13, 14
OH	45	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12
OK	1	0	0	0
OR	2	10,000	99,999	2, 3, 4, 7, 8
PA	29	100	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12
PR	1	10,000	99,999	6, 10
RI	4	1,000	999,999	7, 8, 12
SC	22	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 12

Table 5-2. Facilities that Produce, Process, or Use Antimony Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
TN	18	1,000	999,999	1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14
TX	44	0	499,999,999	1, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	5	10,000	49,999,999	1, 3, 4, 5, 8, 9, 12, 13
VA	7	1,000	999,999	6, 7, 8
VT	1	100,000	999,999	8
WA	2	0	0	0
WI	12	0	999,999	1, 3, 5, 7, 8, 13, 14
WV	4	10,000	99,999	1, 5, 6, 7, 8, 13
WY	1	100,000	999,999	1, 3, 4, 9, 13, 14

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI14 2016 (Data are from 2014)

production of other lead- and tin-based alloys. Secondary antimony production was 17,736 metric tons in 1992, with 1,043 metric tons originating from new scrap and 16,693 metric tons from old scrap (HSDB 2005a; Llewellyn 1989; Plunkert 1982).

The method of treating antimony ore after mining depends on the type of ore and its antimony content. High-grade (45–60%) sulfide ore that is free from lead and arsenic can be extracted by melting using a technique known as liquation. In this process, the ore is heated to 550–660°C in a crucible or reverberatory furnace in a reducing atmosphere. Also, high-grade sulfide ores can be reduced to the metal by a technique in which the ore is heated with iron scrap, known as iron precipitation. The iron replaces the antimony, forming iron sulfide. Another antimony ore treatment technique takes high-grade oxide ores and reduces them with charcoal in a reverberatory furnace. An alkaline flux is used to reduce volatilization losses; loss of antimony due to volatilization can be as high as 12–20%. The method of choice for low-grade (<20%) sulfide ores is volatilizing roasting. In this process, the ore is heated to about 500°C in a controlled amount of oxygen, so that the antimony trioxide formed is volatilized and then recondensed. Intermediate-grade sulfide or oxide ores are generally handled by smelting (Carapella 1978; Herbst et al. 1985). The impure metal may be refined by pyrometallurgical techniques or electrolysis.

5.2 IMPORT/EXPORT

China is the largest exporter of antimony to the United States, most of which is imported as antimony metal. In 2014, total U.S. imports were 365 metric tons for ore and concentrate, 6,210 metric tons for metal, alloys, waste, and scraps, and 17,600 metric tons for antimony oxide. Total U.S. imports were 24,200 metric tons in 2014 and 24,700 metric tons in 2013 (USGS 2015).

The last domestic antimony producing mine in the United States closed in 2001. In 1988, the United States exported 624 metric tons of antimony metal, alloys, and scrap and 1,227 metric tons of antimony oxide (U.S. Bureau of Mines 1989). Canada was the largest recipient of these exports. The United States also exported 942 metric tons of antimony metal, alloy, waste, and scrap in 1992 (HSDB 2005a).

5.3 USE

Pure antimony is a brittle metal and is restricted in its use due to its poor mechanical properties (Grund et al. 2012; HSDB 2005a). As an alloy, it is mixed with other metals to increase their hardness, mechanical strength, corrosion resistance, and electrochemical stability or to decrease their coefficient of friction.

Some antimony alloys expand slightly upon cooling, a valuable property for use in type metal and other castings (Carapella 1978). Antimonial lead is used in small arms ammunition, cable sheathing and lead pipe, and the storage-battery grids, grid plates, straps, and terminals of lead-acid batteries (Grund et al. 2012).

The application of antimony in lead-acid batteries has decreased, and most of the use of antimony in the batteries is in recycling. Historically, antimony improves fluidity and electrical stability, and increases the fatigue strength and creep resistance of the lead in the batteries (Carapella 1978). Alloys of tin and antimony are utilized in electrical equipment, such as the end and side seams of cans, car radiators, and plumbing. Alloys of tin, copper, and antimony are utilized to produce Britannia metal and pewter. Metal products utilize 20% of primary antimony produced (Grund et al. 2012), and 50% of primary antimony is used in plastics to impart flame retardancy. Antimony trioxide is utilized as a flame retardant when combined with a halogen (van Velzen et al. 1998). Antimony is used in the manufacture of chromate pigments, as an opacifer for ceramic glaze, as a gas bubble and color remover in lead crystal glass and glass for television tubes, and as a polymerization catalyst to manufacture polyester fibers (Grund et al. 2012).

Antimony compounds have also been used for the treatment of parasitic diseases such as leishmaniasis. Other antimony salts are used in certain pesticides, ammunition primers, flares, tracer shells, and fireworks, and in the manufacture of disk-brake pads and cutting disks (Grund et al. 2012).

5.4 DISPOSAL

Much of the antimony used in antimonial lead is recycled. This is evident from the large amount of secondary antimony production. Most antimonial lead comes from auto batteries. Little information concerning the disposal of antimony and its compounds has been found in the literature. Wastes from mining and smelting are generally disposed of in landfills. This is evident from the amounts of releases to land from companies that produce antimony and its compounds (Section 6.2.1). In addition, many companies transfer their antimony waste to publicly-owned treatment works or to off-site facilities for disposal. Plastics and articles of clothing that contain small amounts of antimony oxide flame retardants will generally be placed in landfills or undergo incineration along with normal industrial or municipal trash.

Antimony and its compounds have been designated as priority pollutants by EPA (1988). As such, persons who generate, transport, treat, store, or dispose of antimony-containing material must comply with regulations of the federal Resource Conservation and Recovery Act (RCRA). No limitations on the disposal of antimony ore from mines and mills have been promulgated in the Code of Federal Regulations (EPA 1988).

This page is intentionally blank.

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

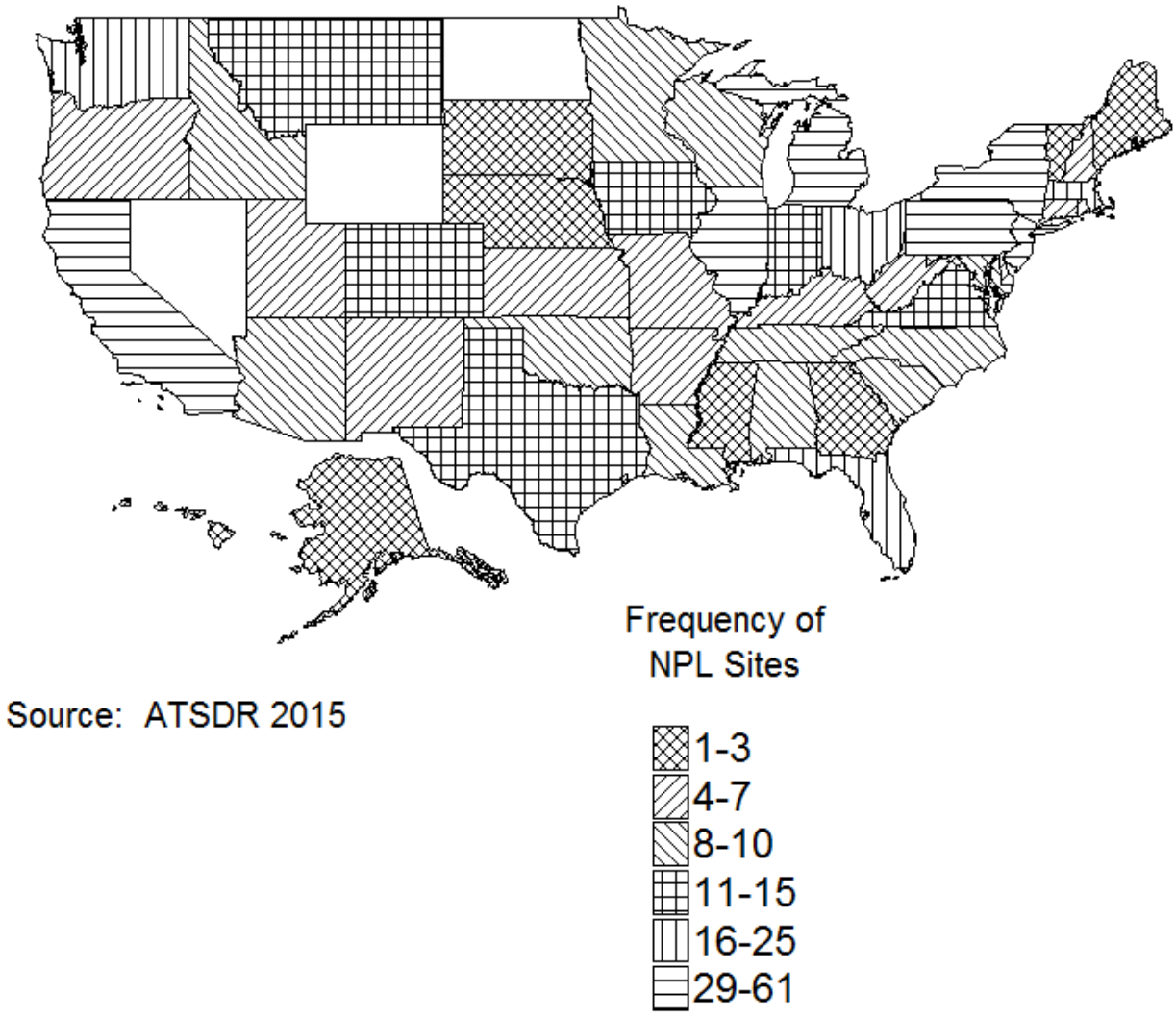
Antimony and antimony-containing compounds have been identified in at least 565 of the 1,832 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). However, the number of sites in which antimony and compounds have been evaluated is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 558 are located within the United States and 4 are located in the Commonwealth of Puerto Rico, 2 are located in the Virgin Islands, and 1 is located in Guam (not shown).

Antimony is a natural constituent of soil and is transported into streams and waterways from natural weathering of soil, as well as from anthropogenic sources (Callahan et al. 1979; Mok and Wai 1990). Antimony is naturally present in the earth's crust at levels of about 0.2–0.3 μg/g (ppm), but these levels vary by location (Telford et al. 2008). Studies indicate that antimony is retained in the soil through adsorption and can sorb onto clay minerals, oxides, and hydroxides in the soil and aquatic sediment (Wilson et al. 2010).

Background levels of antimony in ambient area are typically <20 ng/m^3. However, levels of antimony in ambient air can be >1,000 ng/m^3 near plants that convert antimony ores into metal or manufacture substances such as antimony trioxide (Ragaini et al. 1977).

Background levels of antimony in groundwater in the United States from 1992 to 2003 was low, with median concentrations of <1 μg/L (USGS 2011). Anthropogenic activity such as mining activities, and coal and municipal waste combustion can result in increases in antimony levels in ambient water (Jablonska-Czapla et al. 2014). Most dissolved antimony in natural waters under aerobic conditions is present in the pentavalent oxidation state as antimonate species ($Sb(OH)_6^-$). Anthropogenic emissions commonly contain antimony in the trivalent oxidation state (e.g., antimony trioxide); however, it is unclear how quickly antimonite oxidizes to antimonate under natural conditions. Under anoxic reducing conditions, trivalent species such as $Sb(OH_3)$, $Sb(OH_4)^-$, and $Sb_2S_4^-$ are the most thermodynamically stable forms of antimony.

Figure 6-1. Frequency of NPL Sites with Antimony and Compounds



Source: ATSDR 2015

Antimony can be reduced and methylated by microorganisms in anaerobic sediment, releasing volatile methylated antimony compounds into the water. Multiple microorganisms have been found to methylate antimony in the soil and water and some anoxic or poorly oxygenated environments (Bentley and Chasteen 2002).

The general population is exposed to low levels of antimony in ambient air and food. Individuals can be exposed to antimony in polyethylene terephthalate (PET) water bottles (reviewed in Belzile et al. 2011) or from products containing antimony flame retardants. Occupationally exposed workers will have the highest levels of exposure to antimony (Quiroz et al. 2011; Smith et al. 1995).

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 7,397 pounds (~3 metric tons) of antimony to the atmosphere from 88 domestic manufacturing and processing facilities in 2014, accounted for <1%of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-1. Estimated releases of 22,767 pounds (10 metric tons) of antimony compounds to the atmosphere from 458 domestic manufacturing and processing facilities in 2014, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-2.

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Antimony[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	4	169	577	0	477,514	0	476,851	1,408	478,260
AR	2	49	103	0	0	13,675	152	13,675	13,827
AZ	1	0	0	0	0	0	0	0	0
CA	4	2	23	0	14,489	2	14,241	275	14,517
CT	1	0	0	0	0	239	0	239	239
FL	1	9	0	0	1,664	0	9	1,664	1,673
IA	2	0	0	0	14	0	14	0	14
ID	3	3	1	0	11,716	0	11,720	0	11,720
IL	1	3	0	0	0	No data	3	0	3
IN	3	19	3	0	23,015	9,294	1,033	31,298	32,331
KS	2	14	0	0	0	19	14	19	33
KY	2	1	0	0	0	0	1	0	1
MI	2	10	0	0	3,662	0	10	3,662	3,672
MN	3	7	452	0	43,315	0	7	43,767	43,773
MO	4	8	39	0	361	1,771	353	1,826	2,180
MS	3	1	0	0	3	159	1	162	163
MT	1	5,491	0	0	0	0	5,491	0	5,491
NC	4	18	0	0	5,988	0	3,419	2,587	6,006
NE	3	107	5	0	2,650	36	107	2,691	2,798
NH	1	No data	No data	No data	No data	No data	No data	No data	No data
NJ	2	0	0	0	0	0	0	0	0
NV	2	6	0	0	82,660	4	82,666	4	82,670
NY	2	30	5	0	5	3,625	35	3,630	3,665
OH	12	419	0	0	1,456	1,880	419	3,336	3,755
OR	1	0	0	0	19,713	487	19,713	487	20,200
PA	6	241	253	0	3,508	1,845	358	5,489	5,847
SC	1	4	4	0	101,589	No data	4	101,594	101,598
TN	3	255	255	0	750	224	1,010	474	1,484
TX	5	7	3	0	13,585	0	13,578	17	13,595
VA	3	500	0	0	0	0	500	0	500

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Antimony[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
WA	2	25	5	0	139	0	25	144	169
WI	2	0	0	0	0	0	0	0	0
Total	88	7,397	1,729	0	807,797	33,260	631,735	218,449	850,184

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI14 2016 (Data are from 2014)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Antimony Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	1	0	40	0	13,000	0	13,040	0	13,040
AL	8	100	5	0	3,381	694	105	4,075	4,180
AR	3	58	7	0	2	422	63	426	489
AZ	3	552	10	0	514,372	0	514,874	60	514,934
CA	15	24	407	0	316,758	7,164	62	324,291	324,353
CO	2	165	0	0	4,159	0	165	4,159	4,324
CT	4	15	250	0	6,402	32,499	15	39,151	39,166
DE	1	0	0	0	0	0	0	0	0
FL	2	0	0	0	1,290	0	0	1,290	1,290
GA	22	490	2,075	0	29,165	7,570	500	38,800	39,301
IA	2	6	0	0	250	0	6	250	256
ID	3	1,508	75	0	130,488	0	132,071	0	132,072
IL	21	850	278	24,371	64,978	2,398	55,059	38,071	93,130
IN	27	1,454	6,459	0	592,850	36,733	86,014	551,486	637,500
KS	8	329	5	0	20,975	492	329	21,472	21,801
KY	19	2,236	2,887	0	51,401	31,266	49,072	47,601	96,672
LA	9	733	3,159	0	1,967	5,694	3,906	7,647	11,553
MA	17	651	428	0	9,388	61,972	655	71,784	72,439
MD	1	No data	No data	No data	No data	No data	No data	No data	No data
MI	9	276	98	0	12,691	699	276	13,488	13,764
MN	10	172	3,595	0	14,518	2,495	3,737	17,043	20,779
MO	10	18	4,111	0	232,926	0	214,688	22,367	237,056
MS	11	106	359	0	1,693	30,082	107	32,132	32,240
MT	2	140	0	0	9,240	40	9,380	40	9,420
NC	20	462	259	0	22,653	8,120	971	30,523	31,494
ND	1	56	0	0	125,000	No data	125,056	No data	125,056
NE	5	10	5	0	38,326	1,627	26,028	13,939	39,967
NH	2	1	0	0	2,390	50	1	2,440	2,441
NJ	10	114	13	0	2,827	4,588	119	7,423	7,541
NV	8	53	150	0	3,951,301	382	3,951,504	382	3,951,886
NY	6	28	439	0	66,155	2	1,095	65,529	66,624
OH	45	976	93	239	51,470	15,598	1,218	67,159	68,376
OK	1	No data	No data	No data	No data	No data	No data	No data	No data
OR	2	0	0	0	0	3,361	0	3,361	3,361
PA	29	534	473	0	79,150	32,830	9,789	103,198	112,987
PR	1	10	0	0	62,510	0	10	62,510	62,520
RI	4	33	6	0	7,895	3,600	38	11,496	11,534

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Antimony Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
SC	22	540	3,035	0	16,596	3,111	854	22,427	23,282
TN	18	5,865	1,208	0	33,920	603	22,925	18,671	41,596
TX	44	1,640	1,741	15,418	432,674	40,495	390,539	101,429	491,968
UT	5	344	1,000	0	182,612	10,191	126,830	67,317	194,147
VA	7	70	671	0	11,172	51	91	11,872	11,964
VT	1	0	0	0	0	0	0	0	0
WA	2	No data	No data	No data	No data	No data	No data	No data	No data
WI	10	1,834	9	0	99,136	8,127	1,838	107,269	109,107
WV	4	255	0	0	5,351	5,771	255	11,122	11,377
WY	1	57	0	0	2,358	0	2,415	0	2,415
Total	458	22,767	33,350	40,028	7,225,389	358,214	5,745,701	1,943,699	7,689,400

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI14 2016 (Data are from 2014)

Section 112 of the Clean Air Act (CAA) lists antimony as one of 188 hazardous air pollutants (HAPs) known to cause or suspected of causing cancer or other serious human health effects or ecosystem damage (EPA 2000). EPA's National Emission Inventory (NEI) database contains data regarding sources that emit criteria air pollutants and their precursors, and HAPs for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands (prior to 1999, criteria pollutant emission estimates were maintained in the National Emission Trends [NET] database and HAP emission estimates were maintained in the National Toxics Inventory [NTI] database). The NEI database derives emission data from multiple sources, including state and local environmental agencies; the TRI database; computer models for on-road and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Using composite data from the NTI database from 1990 to 1993, it was estimated that the annual emissions of antimony in the United States were approximately 103 tons per year during that time frame (EPA 2000). Data downloaded from the 2011 NEI (see Table 6-3) indicated that the total emission of antimony was approximately 5,210,763 pounds, with the biggest contribution arising from electric generation by coal (EPA 2016).

Releases of antimony to the atmosphere result from natural and anthropogenic sources. Total emissions from both sources were reported to be 6,100 tons/year in the 1980s; anthropogenic sources such as coal combustion, smelting, and refining were the major sources (Belzile et al. 2011). It was also estimated that 41% of antimony emissions to the air were from natural sources in the 1980s. The natural sources and their median percentage contribution were: wind-borne soil particles, 32.5%; volcanos, 29.6%; sea salt spray, 23.3%; forest fires, 9.2%; and biogenic sources, 12.1% (Nriagu 1989).

Total mid-1990 atmospheric emissions of antimony were reported to be 1,561 tonnes/year total from anthropogenic sources. Emissions from the combustion of fuels, lead production, zinc production, copper production, nonferrous production, pig iron and steel production, municipal waste, and sewage sludge were found to be 319, 134, 95, 547, 7, 235, 34, and 730 tonnes, respectively (Pacyna and Pacyna 2001).

Atmospheric particulate matter was found to be enriched with antimony in Japan; brake abrasion dust from automobiles and waste fly ash were found to be the predominant sources of antimony emissions. Emissions were estimated to be 21 tonnes/year from brake pads (Iijima et al. 2009). Antimony levels in high-density traffic areas are likely due to abrasion of tires, brake lining, and other automotive components that use of antimony alloys (Belzile et al. 2011). In Gottingen, Germany, 176 kg/year of antimony is emitted from brakes, tires, street surfaces, and vehicle exhaust (WHO 2003).

Table 6-3. 2011 National Emission Inventory (NEI) Total National Emissions

Name	Annual emissions (lb)
Bulk gasoline terminals	2.5134
Commercial cooking	264.183
Dust, construction dust	5.26327
Fires, agricultural field burning	330.6032
Fuel combustion, commercial/institutional, biomass	67.40831
Fuel combustion, commercial/institutional, coal	40.24683
Fuel combustion, commercial/institutional, natural gas	0.09
Fuel combustion, commercial/institutional, oil	143.801
Fuel combustion, commercial/institutional, other	1.411491
Fuel combustion, electric generation, biomass	188.6612
Fuel combustion, electric generation, biomass coal	13,020.77
Fuel combustion, electric generation, biomass natural gas	78.23796
Fuel combustion, electric generation, biomass oil	5,978.314
Fuel combustion, electric generation, biomass other	25.92661
Fuel combustion, industrial boilers, internal combustion engines, biomass	2,206.582
Fuel combustion, industrial boilers, internal combustion engines, coal	2,513.459
Fuel combustion, industrial boilers, internal combustion engines, natural gas	1,682.659
Fuel combustion, industrial boilers, internal combustion engines, oil	311.0068
Fuel combustion, industrial boilers, internal combustion engines, other	801.3158
Fuel combustion, residential, natural gas	0
Fuel combustion, residential, oil	0.00051
Fuel combustion, residential, other	0.647524
Industrial processes, cement manufacturing	78.64444
Industrial processes, chemical manufacturing	1,502.073
Industrial processes, ferrous metals	1,071.269
Industrial processes, mining	94.03349
Industrial processes, not elsewhere classified	25,172.5
Industrial processes, nonferrous metals	11,997.31
Industrial processes, oil and gas production	220.7644
Industrial processes, petroleum refineries	2,073.725
Industrial processes, pulp and paper	1,857.656
Industrial processes, storage and transfer	597.7857

Table 6-3. 2011 National Emission Inventory (NEI) Total National Emissions

Name	Annual emissions (lb)
Miscellaneous non-industrial, not elsewhere classified	20.64527
Mobile, commercial marine vessels	69.72685
Mobile, locomotives	314.1618
Solvent, degreasing	416.547
Solvent, graphic arts	19.95
Solvent, industrial surface coating and solvent use	6,836.025
Waste disposal	407.8158
Total	5,210,763

Source: EPA 2016

Increased emissions from fly ash were also reported in Japan. Fly ash is produced in waste incineration (Iijima et al. 2009). Antimony concentrations in fly ash were reported to be 4.7 µg/g total in Japan, 1–3.9 µg/g in various countries, and 1.99 µg/g total in Spain (Smichowski 2008).

6.2.2 Water

Estimated releases of 1,729 pounds (~0.8 metric tons) of antimony to surface water from 88 domestic manufacturing and processing facilities in 2014, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-1. Estimated releases of 33,350 pounds (15 metric tons) of antimony compounds to surface water from 458 domestic manufacturing and processing facilities in 2014, accounted for <1% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-2.

Antimony is a natural constituent of soil and is transported into streams and waterways in runoff either due to natural weathering or disturbed soil (Cole et al. 1984).

Antimony is also found in water due to contamination from mining and smelter, shooting ranges, and road sides that contain dust from brake pads and tires.

6.2.3 Soil

Estimated releases of 807,797 pounds (~366 metric tons) of antimony to soils from 88 domestic manufacturing and processing facilities in 2014, accounted for about 95% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). These releases are summarized in Table 6-1. Estimated releases of 7,225,389 pounds (3,278 metric tons) of antimony compounds to the soil from 458 domestic manufacturing and processing facilities in 2014, accounted for about 94% of the estimated total environmental releases from facilities required to report to the TRI (TRI14 2016). Another 40,028 pounds (18 metric tons) were injected underground. These releases are summarized in Table 6-2.

Antimony is a natural constituent of soil and is produced from the weathering of soil parent materials (Wilson et al. 2010). Contamination of the soil leads to increased concentrations of antimony. Most of the antimony released to the environment is released to land. The industries that release the largest amount of antimony are smelters that produce antimony and antimony trioxide. Much of this release is

slag, which is the residue from smelting operations. Other releases to land include sludge from publicly owned treatment works (POTWs) and municipal refuse (Eckel and Langley 1988).

Antimony was reported to be in 166 of the 1,397 soil samples at the Lawrence Berkeley National Laboratory. The samples were obtained from soil boring sites from the construction of 71 groundwater monitoring wells. A 12% occurrence of antimony was reported, and levels found in the sample site (0.7–22 mg/kg) exceeded the background levels of antimony normally found in the soil (DOE 2009a).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

The oxidized form of antimony, Sb(V), is expected to be the more stable form in the environment; however, Sb(III) is formed under certain environmental conditions (Mitsunobu et al. 2006). Similarly, inorganic species are expected to be more present than organic species of antimony in most environmental systems (Wilson et al. 2010).

Sb(V) corresponds to the octahedral antimonite ion, $Sb(OH)_6^-$, while Sb(III) corresponds to the uncharged antimonous acid, $Sb(OH)_3$ in antimony water systems. In the soil, antimony oxidation state and environmental reactions are largely dependent on the pH, redox conditions, and concentrations of co-occurring reduction agents and oxidants in the system (Wilson et al. 2010).

Antimony can be retained in the soil primarily through adsorption. Antimony can sorb to clay minerals, or to oxides and hydroxides in the soil. Sb(III) sorbs more strongly to manganese (III) oxyhydroxide (MnOOH) than to aluminum hydroxide ($Al(OH)_3$) or iron(III) oxide-hydroxide (FeOOH) (Wilson et al. 2010). Antimony K_d values ranged from 1 to 2,065 L/kg in a sorption study investigating plant uptake of antimony (Nakamaru and Sekine 2008).

Antimony behavior in soil-water systems was found to be dependent on redox conditions in a study evaluating soil collected at different depths at the Ichinokawa mine pit in Ehime, Japan. Decreased antimony concentrations were observed in the soil as the water saturation increased. Sb(V) was found to be stable under reducing conditions. Antimony was found to have a positive correlation with iron and manganese in the soil (Mitsunobu et al. 2006).

Sb(III) was found to bind more strongly to solids than Sb(V) in a study evaluating antimony solubility in soil from shooting ranges. Sorption of antimony was highly dependent on pH. At pH levels <7, Sb(V)

was found to be almost completely sorbed. At pH levels of at least 10, Sb(III) was found to be sorbed. The total release of antimony was found to be much higher than the releases from nickel, copper, bismuth, thallium, and mercury in the soil at the seven Swiss shooting ranges (Johnson et al. 2005).

Miravet et al. (2006) examined the mobility of antimony from coal fly ash. Fly ash, from coal fired power plants, contains a mixture of chemicals that may be distributed to soils, freshwater, seawater, or groundwater. Some portions of fly ash are not extractable or are unavailable under environmental conditions; however, the leachable portion of fly ash has the potential to accumulate in organisms. Antimony was found to leach out of fly ash solution at pH 1–12. Sb(V) was the major antimony species in the leachate. Antimony was partially soluble at pH 5, and more soluble at acidic pH values.

Leaching experiments performed with river sediment samples from a mining district in Idaho also indicated that Sb(V) was the major species released during leaching (Mok and Wai 1990). The fraction of antimony leached from sediment with deionized water after 10 days was highly correlated with the free iron and manganese oxide content of the sediment (correlation coefficients of 0.90 and 0.75, respectively). Experiments on the pH dependence of leaching showed marked differences between trivalent and pentavalent antimony (Mok and Wai 1990). The release of trivalent antimony from the sediment increased at low pH; in contrast, the release of pentavalent antimony from sediment increased sharply at high pH (pH 11.4). At pH 4.3, the concentrations of tri- and pentavalent antimony were comparable. Antimony does not appear to bioconcentrate appreciably in fish and aquatic organisms. No detectable bioconcentration occurred during a 28-day test in bluegills (EPA 1980). Only low levels of antimony have been reported in fish and aquatic organisms collected off the coast of Africa, Australia, and the Danube River in Austria (Callahan et al. 1979; Maher 1986). Bioconcentration factors for antimony ranged from 0.15 to 390 (Acquire 1989; Callahan et al. 1979).

Antimony sorption was studied in relation to its plant uptake. Antimony K_d values ranged from 1 to 2,065 L/kg. The K_d values were significantly decreased with increasing phosphate concentrations, indicating that the addition of phosphate fertilizer may increase the potential for antimony uptake in plants. No difference in antimony sorption to soil occurred when sulfates were added to the soil in this study (Nakamaru and Sekine 2008).

Antimony can be taken up by plants through the roots and via surface deposition from aerosols. Surface deposition is the major pathway for soil-to-plant transfer of antimony in field conditions (Tschan et al. 2009).

The *Viola* species were found to accumulate antimony in their roots, stems, leaves, flowers, and seeds. Mean antimony concentrations in *Viola allcharensis* were 0.46 mg/kg in the root, 0.34 mg/kg in the stem, 0.46 mg/kg in the leaf, 0.25 mg/kg in the flower, and 0.40 mg/kg in the seed. Mean antimony concentrations for the root, stem, leaves, flowers, and seeds of *Viola arsenica* were reported as 1.06, 0.25, 0.72, 0.47, and 0.91 mg/kg, respectively. Mean antimony concentrations for *Viola macedonica* were 0.25 mg/kg for each root, stem, leaves, and flowers (Baceva et al. 2014).

Certain plants may be used in phytoremediation because they are able to accumulate metals in their tissues and have a high tolerance for those metals in contaminated soils. In the Sao Domingos copper mine, several plant species were found to accumulate antimony in their systems. Concentrations of antimony in the mine tailings ranged from 203 to 2,513 mg/kg. Concentrations in plant species were 6.67 mg/kg for *Erica andevalensis*, 4.09 mg/kg for *Erica australis,* 3.59 mg/kg for *Corrigiola telephypholia*, 2.8 mg/kg for *Echium* plantagium, 2.02 mg/kg for *Eritrae pulcheria*, and 0.60 mg/kg for *Daphne gnidium* and other plants (Anawar et al. 2011).

Root tissues of Maize (*Zea mays*) contained 0.35, 2.5, 3.98, 22.01, and 26.5–68.42 mg/kg of antimony, when exposed to 10, 50, 100, 500 and 1,000 mg/kg of antinomy, respectively. Concentrations of antimony at 10, 50, 100, 500, and 1,000 mg/kg corresponded to 0.82, 6.32, 13.76, 45.1, and 68.42 mg/kg in the shoot tissues. Higher concentrations of antimony resulted in higher antimony accumulation in the plants in this study (Pan et al. 2010).

In a similar study, antimony uptake was measured in maize (*Z. mays*) and sunflowers (*Helianthus annuus*). No significant differences in uptake between the two plant species were observed. The bioaccumulation coefficient was reported as 0.93 for maize and 1.33 for sunflower (Tschan et al. 2008).

The mechanism of Baker yeast cell (*Saccharomyces cerevisiae*) antimony biosorption has also been investigated. Sb(III) was removed from contaminated aqueous samples and accumulated in the Baker yeast cells. Accumulation increased with increasing pH, incubation time, temperature, and amount of yeast. Sb(V) was undisturbed under the conditions of the test, indicating selective accumulation of Sb(III) (Perez-Corona et al. 1997).

6.3.2 Transformation and Degradation

6.3.2.1 Air

Little is known about the chemical forms and physical and chemical transformations of trace elements in the atmosphere. This is primarily because analytical methods provide information concerning the metal content rather than the specific compounds or species. In the absence of specific information, it is generally assumed that elements of anthropogenic origin, especially those emanating from combustion sources, are present as the oxide. Windblown dust particles may contain antimony in mineral species, such as sulfides and oxides, and are associated with silicates. When released into the atmosphere as an aerosol, antimony is believed to be oxidized to antimony trioxide by reaction with atmospheric oxidants.

6.3.2.2 Water

Most of the dissolved antimony in natural waters is present in the pentavalent oxidation state as the antimonate species ($Sb(OH)_6^-$) under aerobic conditions (Filella et al. 2002). Anthropogenic emissions commonly contain antimony in the trivalent oxidation state (antimonite; e.g., antimony trioxide); however, it is not certain how quickly antimonite oxidizes to antimonate under natural conditions. Under anoxic reducing conditions, trivalent species, such as $Sb(OH_3)$, $Sb(OH_4)^-$ and $Sb_2S_4^-$, are the most thermodynamically stable forms.

The pentavalent form was reported to be the predominant species in a study examining the behavior of antimony in oxic systems (Filella et al. 2002). The trivalent form was also found to be sometimes present in oxic systems; however, >10% of the total dissolved amount of antimony was rarely found to be in the trivalent form (Filella et al. 2009a). Antimony speciation in various types of natural waters was analyzed in a study conducted in Warsaw Poland. Of the 12 samples obtained from the different rivers, lakes, and ponds, the majority of the total antimony, or 96–99%, was in the pentavalent form (Garbos et al. 2000).

Han-Wen et al. (1982) estimated the rate of oxidation of the trivalent form to the pentavalent form by adding known quantities of each into lake water and waste water samples and studying the change in concentration with respect to time. The trivalent form of antimony in lake water and waste water appeared to be unstable since none could be detected after 6 hours; it is presumed that there were oxidants in the water samples. The addition of tartaric acid (1% w/v) into the water samples had a stabilizing effect (no changes in Sb(III) levels) after 5 days due to the fact that the rate of conversion of Sb(III) into Sb(V) decreases with increasing acidity.

Cutter (1992) estimated a much slower oxidation rate of trivalent antimony in seawater by measuring the depth profiles for antimony species in the upper 100 m of the Black sea. No Sb(III) was detected in the upper surface levels, but a gradual increase of Sb(III) concentration with a gradual decrease in Sb(V) levels was observed with increasing depth beyond 60 m. The maximum concentration of Sb(III) was observed in the largely anaerobic region (90–100 m). At this depth, no pentavalent antimony was detectable. An estimated pseudo first-order oxidation rate constant of 0.008 day^{-1} was calculated from these data, corresponding to a residence time (1/rate constant) of about 125 days. This rate included all forms of removal since Sb(III) may also be scavenged by suspended particulate matter in the water column. It is presumed that the presence of the thermodynamically unstable trivalent species in aerobic waters may, in part, be due to biotic processes involving the uptake of antimonate and the subsequent biological conversion to the trivalent species. These unstable species were reported to be able to persist due to the low rates of conversion (Cutter 1992). Likewise, as the trivalent species may be present in thermodynamically unfavorable (aerobic) environments, the pentavalent species has also been detected in anoxic settings. As reported by Cutter (1992), the presence of pentavalent antimony in anoxic waters of the Baltic Sea, the Black Sea, and the Saanich Inlet has been observed, and is due to the transport of Sb(V) on sinking detritus from aerobic waters, formation of thioantimonate species, and advection of surface waters containing high levels of pentavalent antimony. All of these potential transport processes also assume a slow reduction rate of pentavalent conversion to the trivalent form. The rate constant for this reaction was estimated as 1.1×10^{-6} $days^{-1}$ (Cutter 1992).

Antimony can be reduced and methylated by microorganisms in the aquatic environment, similar to arsenic, and become mobilized (Andreae et al. 1983; Austin and Millward 1988). This reaction is most likely to occur in reducing environments, such as in bed sediment.

Pseudomonas fluorescens K27, isolated from the Kesterson reservoir in California, was found to reduce trimethyldibromoantimony to trimethylstibine (Bentley and Chasteeen 2002). Sb(III) and methylated antimony species were converted to stibine at approximately pH 7; however, Sb(V) was not converted. Sb(III) was found to be oxidized in an *Agrobacterium tumefaciens* isolate. The algal strain 5508, found at the Yellowstone National Park in the geothermal environment of Dragon Spring, was also found to have the capability to oxidize Sb(III) (Lehr et al. 2007).

The oxidation rate of As(III) and Sb(III) was studied using circumneutral pH (pH 5.5–6.5) and acidic conditions similar to those in mine tailings under both abiotic and biotic conditions. Under acidic

conditions, both antimony and arsenic were slowly oxidized, but more rapid oxidation was observed in aerated abiotic solutions containing Fe(III) as opposed to solutions containing microbes; this process was accelerated by natural sunlight and increasing chloride ion concentration (Asta et al. 2012). In unfiltered (microbially active) circumneutral water, antimony was oxidized at a similar rate as in the acidic solutions; however, the rate of arsenic oxidation was enhanced and was several orders of magnitude greater than the rate of antimony oxidation.

6.3.2.3 Sediment and Soil

Transformation of antimony in the soil is dependent on the microbial population (Luo et al. 2014). Anaerobic microbial methylation occurs in the soil, producing trimethylstibine. Trimethylstibine was produced by the pure cultures of *Clostridium collagenovorans* and *Desulfovibrio vulgaris* under anaerobic conditions in sewage sludge. Anaerobic digestion of sewage sludge by *Methanobacterium formicicum* formed stibine, monomethylstibine, dimethylstibine, and trimethylstibine (Michalke et al. 2000). Under aerobic conditions, *Scopulariopsis brevicaulis* was found to methylate antimony through a dimethylantimony species intermediate in the trimethylstibine pathway (Bentley and Chasteen 2002).

Five soil samples were collected in an antimony and arsenic mine field in the Hunan Province of China. It was determined that *Gemmatimonadetes* and *Actinobacteria* aid in the bioremediation of antimony in the mine field soil (Luo et al. 2014).

6.3.2.4 Other Media

A 1998 study detected antimony in infant cot mattress covers that contained polyvinyl chloride (PVC). Antimony leached into extraction fluids from mattress samples (Jenkins et al. 1998). In the mid-1990s, it was hypothesized that microbial growth on the cot mattress could generate stibines from the antimony trioxide in the flame retardants. It was also hypothesized that the stibine could result in sudden infant death syndrome (SIDS) (Richardson 1994). However, increases in liver and brain antimony levels have not been found in infants dying from SIDS, as compared to infants dying from other causes (Boex et al. 1998; Cullen et al. 2000).

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to antimony depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of

antimony in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on antimony levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring antimony in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Background levels of antimony in ambient air are usually on the order of about 1 ng/m^3, but can be higher in urban environments. In the vicinity of plants that convert antimony ores into metal (smelting operations), or other point sources, levels can be >1,000 ng/m^3.

The Air Quality System (AQS) database is EPA's repository of criteria air pollutant and HAPs monitoring data. Detailed air monitoring data for antimony in various cities in the United States for 2014 are shown in Table 6-4. Data for other years are available and may be accessed directly from the EPA website. Daily mean concentrations ranged from 0.37 to 2 ng/m^3 for antimony (total suspended particulate; TSP) standard temperature and pressure (STP); 0.13–20.6 ng/m^3 for antimony PM_{10} LC (local conditions); 0.56–2.18 ng/m^3 for antimony PM_{10} STP; and 1.9–22 ng/m^3 for antimony $PM_{2.5}$ LC (EPA 2015a).

Antimony concentrations over the North Atlantic and North Pacific were 0.086 and 0.0037 ng/m^3, respectively (Arimoto and Duce 1987; Austin and Millward 1988). Two values reported for antimony in aerosols in clean continental and marine environments were 0.2 ng/m^3 at the Jungfraujoch in the Swiss Alps and 0.00045 ng/m^3 at American Samoa (Austin and Millward 1988). The MMAD of antimony-containing aerosols from a range of areas remote from anthropogenic sources was 0.86 μm (Milford and Davidson 1985). The mass size distribution is bimodal, with the larger peak at about 0.6 μm and a smaller one at about 3 μm. An example of the size distribution of antimony-containing particles removed from anthropogenic sources was obtained in an 8-week study on an island in the German Bight. The concentration of antimony in a size fraction increased as the size decreased. The antimony concentration ranged from 0.03 ng/m^3 for particles >7.2 μm to 0.3 ng/m^3 for particles <0.5 μm (Stoessel and Michaelis 1986).

Table 6-4. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony (TSP) STP	Rosemount, Minnesota	27	0
Antimony (TSP) STP	Eagan, Minnesota	26	1.429
Antimony (TSP) STP	Eagan, Minnesota	28	2
Antimony (TSP) STP	Apple Valley, Minnesota	25	0.417
Antimony (TSP) STP	Minneapolis, Minnesota	24	1.6
Antimony (TSP) STP	Minneapolis, Minnesota	25	0.385
Antimony (TSP) STP	Minneapolis, Minnesota	26	0.37
Antimony (TSP) STP	Minneapolis, Minnesota	27	0
Antimony (TSP) STP	St. Paul, Minnesota	27	0
Antimony (TSP) STP	Virginia, Minnesota	27	0
Antimony (TSP) STP	Duluth, Minnesota	22	0.4
Antimony (TSP) STP	Duluth, Minnesota	25	0.4
Antimony (TSP) STP	Newport, Minnesota	25	0
Antimony (TSP) STP	Bayport, Minnesota	27	0
Antimony (TSP) STP	Yukon, Oklahoma	28	0.425
Antimony (TSP) STP	Oklahoma City, Oklahoma	40	0.5
Antimony (TSP) STP	Tulsa, Oklahoma	40	0.667
Antimony (TSP) STP	Tulsa, Oklahoma	39	0.59
Antimony (TSP) STP	Tulsa, Oklahoma	39	0.789
Antimony (TSP) STP	Tulsa, Oklahoma	38	0.784
Antimony PM_{10} LC	Phoenix, Arizona	44	2.450909
Antimony PM_{10} LC	Middletown, California	45	4.511111
Antimony PM_{10} LC	Cobb, California	45	4.444444
Antimony PM_{10} LC	Banning, California	10	1.05
Antimony PM_{10} LC	San Jose, California	45	2.463111
Antimony PM_{10} LC	Valrico, Florida	15	1.46
Antimony PM_{10} LC	Valrico, Florida	15	1.58
Antimony PM_{10} LC	Boston, Massachusetts	39	1.51
Antimony PM_{10} LC	Boston, Massachusetts	23	1.49087
Antimony PM_{10} LC	St. Louis, Missouri	3,705	20.64183
Antimony PM_{10} LC	St. Louis, Missouri	40	1.74975
Antimony PM_{10} LC	St. Louis, Missouri	40	1.7335
Antimony PM_{10} LC	Underhill (Town of), Vermont	14	0.133571
Antimony PM_{10} LC	Underhill (Town of), Vermont	3	0.25
Antimony PM_{10} LC	Seattle, Washington	40	1.0185
Antimony PM_{10} STP	Orlando, Florida	22	0.754545
Antimony PM_{10} STP	Saint Petersburg, Florida	43	0.635349
Antimony PM_{10} STP	Pinellas Park, Florida	45	0.697556
Antimony PM_{10} STP	Northbrook, Illinois	27	0.681111
Antimony PM_{10} STP	Ashland, Kentucky	34	2.182353

Table 6-4. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony PM_{10} STP	Ashland, Kentucky	2	1.3
Antimony PM_{10} STP	Kentucky	33	0.562727
Antimony PM_{10} STP	Kentucky	15	1.012667
Antimony PM_{10} STP	Lexington-Fayette (corporate name for Lexington), Kentucky	33	1.047879
Antimony PM_{10} STP	Kentucky	34	0.754118
Antimony PM_{10} STP	Calvert City (RR name Calvert), Kentucky	32	0.59375
Antimony PM_{10} STP	Providence, Rhode Island	50	0.6466
Antimony PM_{10} STP	Providence, Rhode Island	24	0.631667
Antimony PM_{10} STP	Houston, Texas	88	0.647727
Antimony $PM_{2.5}$ LC	Birmingham, Alabama	80	19.213
Antimony $PM_{2.5}$ LC	Birmingham, Alabama	76	18.539
Antimony $PM_{2.5}$ LC	Huntsville, Alabama	39	20.115
Antimony $PM_{2.5}$ LC	Montgomery, Alabama	41	17.768
Antimony $PM_{2.5}$ LC	Phenix City, Alabama	41	20.732
Antimony $PM_{2.5}$ LC	Fairbanks, Alaska	82	19.854
Antimony $PM_{2.5}$ LC	Fairbanks, Alaska	70	20.95
Antimony $PM_{2.5}$ LC	Alaska	30	24.15
Antimony $PM_{2.5}$ LC	Phoenix, Arizona	83	20.729
Antimony $PM_{2.5}$ LC	Tucson, Arizona	71	21.092
Antimony $PM_{2.5}$ LC	North Little Rock, Arkansas	81	20.259
Antimony $PM_{2.5}$ LC	Chico, California	47	10.383
Antimony $PM_{2.5}$ LC	Fresno, California	80	20.344
Antimony $PM_{2.5}$ LC	Calexico, California	39	15.897
Antimony $PM_{2.5}$ LC	Los Angeles, California	81	19.722
Antimony $PM_{2.5}$ LC	Portola, California	45	11.044
Antimony $PM_{2.5}$ LC	Rubidoux, California	79	19.241
Antimony $PM_{2.5}$ LC	Rubidoux, California	41	18.683
Antimony $PM_{2.5}$ LC	Arden-Arcade, California	84	19.929
Antimony $PM_{2.5}$ LC	Sacramento, California	46	12.109
Antimony $PM_{2.5}$ LC	El Cajon, California	17	19.529
Antimony $PM_{2.5}$ LC	Escondido, California	47	10.723
Antimony $PM_{2.5}$ LC	San Jose, California	72	19.326
Antimony $PM_{2.5}$ LC	Modesto, California	47	12.213
Antimony $PM_{2.5}$ LC	Visalia, California	47	11.106
Antimony $PM_{2.5}$ LC	Commerce City, Colorado	38	18.579
Antimony $PM_{2.5}$ LC	Colorado	69	20.457
Antimony $PM_{2.5}$ LC	Platteville, Colorado	35	17.529
Antimony $PM_{2.5}$ LC	New Haven, Connecticut	68	18.904
Antimony $PM_{2.5}$ LC	Dover, Delaware	13	19.615

Table 6-4. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony $PM_{2.5}$ LC	Wilmington, Delaware	62	18.468
Antimony $PM_{2.5}$ LC	Washington, District Of Columbia	78	22.045
Antimony $PM_{2.5}$ LC	Davie, Florida	45	18.944
Antimony $PM_{2.5}$ LC	Valrico, Florida	79	20.101
Antimony $PM_{2.5}$ LC	Tallahassee, Florida	39	18.923
Antimony $PM_{2.5}$ LC	Pinellas Park, Florida	39	20.244
Antimony $PM_{2.5}$ LC	Macon, Georgia	42	18.429
Antimony $PM_{2.5}$ LC	Athens (corporation name Athens-Clarke County), Georgia	42	22.083
Antimony $PM_{2.5}$ LC	Georgia	42	21.643
Antimony $PM_{2.5}$ LC	Georgia	68	19.478
Antimony $PM_{2.5}$ LC	Georgia	40	20.05
Antimony $PM_{2.5}$ LC	Columbus (Remainder), Georgia	41	22.695
Antimony $PM_{2.5}$ LC	Augusta-Richmond County (Remainder), Georgia	34	21.382
Antimony $PM_{2.5}$ LC	Georgia	41	19.805
Antimony $PM_{2.5}$ LC	Hawaii	66	19.712
Antimony $PM_{2.5}$ LC	Idaho	80	20.438
Antimony $PM_{2.5}$ LC	Chicago, Illinois	42	22.405
Antimony $PM_{2.5}$ LC	Chicago, Illinois	75	20.907
Antimony $PM_{2.5}$ LC	Northbrook, Illinois	74	18.507
Antimony $PM_{2.5}$ LC	Naperville, Illinois	38	18.013
Antimony $PM_{2.5}$ LC	Granite City, Illinois	22	20.75
Antimony $PM_{2.5}$ LC	Roxana, Illinois	39	19.692
Antimony $PM_{2.5}$ LC	Belleville, Illinois	38	20.605
Antimony $PM_{2.5}$ LC	Jeffersonville, Indiana	41	19.22
Antimony $PM_{2.5}$ LC	Jasper, Indiana	41	20.232
Antimony $PM_{2.5}$ LC	Elkhart, Indiana	41	18.963
Antimony $PM_{2.5}$ LC	Middletown, Indiana	41	19.402
Antimony $PM_{2.5}$ LC	Gary, Indiana	39	19.372
Antimony $PM_{2.5}$ LC	Indianapolis (Remainder), Indiana	60	20.192
Antimony $PM_{2.5}$ LC	Evansville, Indiana	42	18.774
Antimony $PM_{2.5}$ LC	Cedar Rapids, Iowa	41	18.159
Antimony $PM_{2.5}$ LC	Des Moines, Iowa	41	18.11
Antimony $PM_{2.5}$ LC	Davenport, Iowa	81	20.302
Antimony $PM_{2.5}$ LC	Wichita, Kansas	42	19
Antimony $PM_{2.5}$ LC	Kansas City, Kansas	69	20.645
Antimony $PM_{2.5}$ LC	Ashland, Kentucky	42	20.571
Antimony $PM_{2.5}$ LC	Kentucky	41	17.5
Antimony $PM_{2.5}$ LC	Lexington-Fayette (corporate name for Lexington), Kentucky	42	19.726

Table 6-4. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony $PM_{2.5}$ LC	Louisville, Kentucky	81	20.951
Antimony $PM_{2.5}$ LC	Shreveport, Louisiana	39	18.205
Antimony $PM_{2.5}$ LC	Baton Rouge, Louisiana	76	18.941
Antimony $PM_{2.5}$ LC	Essex, Maryland	75	19.687
Antimony $PM_{2.5}$ LC	Beltsville, Maryland	82	21.451
Antimony $PM_{2.5}$ LC	Chicopee, Massachusetts	80	20.819
Antimony $PM_{2.5}$ LC	Boston, Massachusetts	84	20.077
Antimony $PM_{2.5}$ LC	Boston, Massachusetts	42	18.333
Antimony $PM_{2.5}$ LC	Grand Rapids, Michigan	82	20.951
Antimony $PM_{2.5}$ LC	Tecumseh, Michigan	42	19.583
Antimony $PM_{2.5}$ LC	Michigan	42	20.952
Antimony $PM_{2.5}$ LC	Michigan	42	19.512
Antimony $PM_{2.5}$ LC	Port Huron, Michigan	42	20.298
Antimony $PM_{2.5}$ LC	Allen Park, Michigan	81	20.062
Antimony $PM_{2.5}$ LC	Detroit, Michigan	41	18.402
Antimony $PM_{2.5}$ LC	Dearborn, Michigan	42	18.607
Antimony $PM_{2.5}$ LC	Blaine, Minnesota	82	20.043
Antimony $PM_{2.5}$ LC	Minneapolis, Minnesota	83	20.596
Antimony $PM_{2.5}$ LC	Rochester, Minnesota	42	19.738
Antimony $PM_{2.5}$ LC	Jackson, Mississippi	66	20.818
Antimony $PM_{2.5}$ LC	Missouri	82	22.079
Antimony $PM_{2.5}$ LC	Arnold, Missouri	82	20.152
Antimony $PM_{2.5}$ LC	Missouri	78	21.269
Antimony $PM_{2.5}$ LC	St. Louis, Missouri	81	20.16
Antimony $PM_{2.5}$ LC	Montana	68	19.096
Antimony $PM_{2.5}$ LC	Butte-Silver Bow (Remainder), Montana	53	19.519
Antimony $PM_{2.5}$ LC	Omaha, Nebraska	71	19.873
Antimony $PM_{2.5}$ LC	Sunrise Manor, Nevada	70	19.514
Antimony $PM_{2.5}$ LC	Reno, Nevada	66	19.955
Antimony $PM_{2.5}$ LC	Camden, New Jersey	68	19.831
Antimony $PM_{2.5}$ LC	Newark, New Jersey	68	20.368
Antimony $PM_{2.5}$ LC	North Brunswick Township, New Jersey	66	20.515
Antimony $PM_{2.5}$ LC	North Brunswick Township, New Jersey	38	18.842
Antimony $PM_{2.5}$ LC	Chester, New Jersey	68	19.625
Antimony $PM_{2.5}$ LC	Elizabeth, New Jersey	69	18.725
Antimony $PM_{2.5}$ LC	Albuquerque, New Mexico	84	19.5
Antimony $PM_{2.5}$ LC	Albany, New York	79	18.025
Antimony $PM_{2.5}$ LC	New York, New York	72	18.535
Antimony $PM_{2.5}$ LC	Buffalo, New York	38	18.526
Antimony $PM_{2.5}$ LC	New York	42	19.274

Table 6-4. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony $PM_{2.5}$ LC	Rochester, New York	80	22.65
Antimony $PM_{2.5}$ LC	New York, New York	82	19.024
Antimony $PM_{2.5}$ LC	New York, New York	84	19.964
Antimony $PM_{2.5}$ LC	New York	80	20.556
Antimony $PM_{2.5}$ LC	Asheville, North Carolina	29	17.534
Antimony $PM_{2.5}$ LC	Hickory, North Carolina	12	24.917
Antimony $PM_{2.5}$ LC	Lexington, North Carolina	40	18.838
Antimony $PM_{2.5}$ LC	Winston-Salem, North Carolina	38	19.842
Antimony $PM_{2.5}$ LC	Charlotte, North Carolina	84	19.143
Antimony $PM_{2.5}$ LC	Rockwell, North Carolina	42	18.202
Antimony $PM_{2.5}$ LC	Raleigh, North Carolina	78	19.391
Antimony $PM_{2.5}$ LC	North Dakota	84	19.048
Antimony $PM_{2.5}$ LC	Cleveland, Ohio	38	22.013
Antimony $PM_{2.5}$ LC	Cleveland, Ohio	66	21.356
Antimony $PM_{2.5}$ LC	Cleveland, Ohio	36	20.75
Antimony $PM_{2.5}$ LC	Columbus, Ohio	42	18.75
Antimony $PM_{2.5}$ LC	Cincinnati, Ohio	83	19.88
Antimony $PM_{2.5}$ LC	Steubenville, Ohio	36	19.944
Antimony $PM_{2.5}$ LC	Ironton, Ohio	42	19.048
Antimony $PM_{2.5}$ LC	Sheffield, Ohio	41	22.61
Antimony $PM_{2.5}$ LC	Toledo, Ohio	37	18.432
Antimony $PM_{2.5}$ LC	Youngstown, Ohio	30	19.333
Antimony $PM_{2.5}$ LC	Dayton, Ohio	36	18.819
Antimony $PM_{2.5}$ LC	New Paris, Ohio	83	20.524
Antimony $PM_{2.5}$ LC	Canton, Ohio	41	19.341
Antimony $PM_{2.5}$ LC	Akron, Ohio	35	19.243
Antimony $PM_{2.5}$ LC	Oklahoma City, Oklahoma	40	18.538
Antimony $PM_{2.5}$ LC	Tulsa, Oklahoma	81	19.914
Antimony $PM_{2.5}$ LC	Altamont, Oregon	26	13.596
Antimony $PM_{2.5}$ LC	Altamont, Oregon	3	11.6
Antimony $PM_{2.5}$ LC	Lakeview, Oregon	30	13.482
Antimony $PM_{2.5}$ LC	Lakeview, Oregon	3	11.6
Antimony $PM_{2.5}$ LC	Eugene, Oregon	30	12.715
Antimony $PM_{2.5}$ LC	Eugene, Oregon	3	11.583
Antimony $PM_{2.5}$ LC	Portland, Oregon	71	19.993
Antimony $PM_{2.5}$ LC	Pennsylvania	41	20.378
Antimony $PM_{2.5}$ LC	Pittsburgh, Pennsylvania	70	19.164
Antimony $PM_{2.5}$ LC	Liberty, Pennsylvania	42	20.024
Antimony $PM_{2.5}$ LC	Pennsylvania	42	19.369
Antimony $PM_{2.5}$ LC	Johnstown, Pennsylvania	42	17.119

Table 6-4. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony $PM_{2.5}$ LC	State College, Pennsylvania	37	20.378
Antimony $PM_{2.5}$ LC	Pennsylvania	28	17.732
Antimony $PM_{2.5}$ LC	Pennsylvania	40	18.8
Antimony $PM_{2.5}$ LC	Erie, Pennsylvania	40	20.2
Antimony $PM_{2.5}$ LC	Scranton, Pennsylvania	22	18.25
Antimony $PM_{2.5}$ LC	Lancaster, Pennsylvania	42	20.75
Antimony $PM_{2.5}$ LC	Freemansburg, Pennsylvania	37	18.541
Antimony $PM_{2.5}$ LC	Philadelphia, Pennsylvania	79	21.285
Antimony $PM_{2.5}$ LC	Philadelphia, Pennsylvania	42	19.607
Antimony $PM_{2.5}$ LC	Pennsylvania	39	18.128
Antimony $PM_{2.5}$ LC	Greensburg, Pennsylvania	38	18.684
Antimony $PM_{2.5}$ LC	York, Pennsylvania	41	21.561
Antimony $PM_{2.5}$ LC	East Providence, Rhode Island	80	19.894
Antimony $PM_{2.5}$ LC	South Carolina	36	17.597
Antimony $PM_{2.5}$ LC	Greenville, South Carolina	39	19.936
Antimony $PM_{2.5}$ LC	Dentsville (Dents), South Carolina	83	19.602
Antimony $PM_{2.5}$ LC	Sioux Falls, South Dakota	74	19.818
Antimony $PM_{2.5}$ LC	Nashville, Tennessee	41	21.988
Antimony $PM_{2.5}$ LC	Chattanooga, Tennessee	42	19.512
Antimony $PM_{2.5}$ LC	Knoxville, Tennessee	40	20.3
Antimony $PM_{2.5}$ LC	Loretto, Tennessee	41	20.988
Antimony $PM_{2.5}$ LC	Memphis, Tennessee	79	18.899
Antimony $PM_{2.5}$ LC	Dallas, Texas	86	2.033
Antimony $PM_{2.5}$ LC	Dallas, Texas	82	20.683
Antimony $PM_{2.5}$ LC	Midlothian, Texas	44	2.002
Antimony $PM_{2.5}$ LC	El Paso, Texas	75	21.407
Antimony $PM_{2.5}$ LC	Texas	46	1.972
Antimony $PM_{2.5}$ LC	Deer Park, Texas	83	19.813
Antimony $PM_{2.5}$ LC	Deer Park, Texas	42	18.595
Antimony $PM_{2.5}$ LC	Texas	41	18.817
Antimony $PM_{2.5}$ LC	Corpus Christi, Texas	42	1.993
Antimony $PM_{2.5}$ LC	Bountiful, Utah	41	18.512
Antimony $PM_{2.5}$ LC	Salt Lake City, Utah	74	21.378
Antimony $PM_{2.5}$ LC	Lindon, Utah	41	22.854
Antimony $PM_{2.5}$ LC	Burlington, Vermont	56	20.813
Antimony $PM_{2.5}$ LC	East Highland Park, Virginia	62	19.435
Antimony $PM_{2.5}$ LC	Vancouver, Washington	42	19.488
Antimony $PM_{2.5}$ LC	Seattle, Washington	77	20.052
Antimony $PM_{2.5}$ LC	Tacoma, Washington	39	17.731
Antimony $PM_{2.5}$ LC	Marysville, Washington	38	20.763

Table 6-4. Median Antimony Levels in Ambient Air

Antimony type	Sampling location	Number of samples	Daily mean concentration (ng/m^3)
Antimony $PM_{2.5}$ LC	Yakima, Washington	42	19.952
Antimony $PM_{2.5}$ LC	West Virginia	70	19.636
Antimony $PM_{2.5}$ LC	South Charleston, West Virginia	13	18.846
Antimony $PM_{2.5}$ LC	Moundsville, West Virginia	27	18.185
Antimony $PM_{2.5}$ LC	Green Bay, Wisconsin	41	18.951
Antimony $PM_{2.5}$ LC	Horicon, Wisconsin	84	19.75
Antimony $PM_{2.5}$ LC	Milwaukee, Wisconsin	79	19.101
Antimony $PM_{2.5}$ LC	Wisconsin	42	18.881
Antimony $PM_{2.5}$ LC	Waukesha, Wisconsin	41	20.061
Antimony $PM_{2.5}$ LC	Wyoming	82	19.384

LC = local conditions; PM = particulate matter; STP = standard temperature and pressure; TSP = total suspended particulate

Source: EPA 2015a

Antimony is enriched in coal and vaporized in fossil fuel combustion, resulting in the release of increased levels of antimony to the atmosphere. After condensation, antimony is primarily found in fly ash (Miravet et al. 2006). Antimony levels in coal fly ash leachates from two different samples obtained from the Escucha coal-fired power station in Teruel, Spain were reported to be 0.01–0.07 µg/g for Sb(III) and 0.17–0.41 µg/g for Sb(V) in the first sample. Levels were slightly higher in the second sample: Sb(III) levels were 0.02–0.09 µg/g and Sb(V) levels were 0.16–0.56 µg/g. The data indicate that Sb(V) was the predominant species found in the leachate, and while the antimony was found to bind strongly to the matrix, the study demonstrated that significant amounts of antimony can leach out of coal fly ash particles (Miravet et al. 2006). Likewise, in Taipei, Taiwan, the total antimony content in fly ash was 4.7 µg/g, while in Barcelona, Spain, the Sb(III) content was 0.07–0.36 µg/g and the Sb(V) content was 1.63 µg/g. Antimony content (predominantly Sb(III)) in fly ash from various countries ranged from 1 to 3.9 µg/g (Smichowski 2008). Antimony emissions may have increased in Japan over the years due to the fact that part of the process in the incineration of household wastes containing plastics occurs in Japan; thus, fly ash originating from waste incineration may be an important source of antimony (Iijima et al. 2009).

Several older studies show that antimony can travel long distances, and that ambient levels may reflect the origin of the air masses. The geometric mean antimony concentrations in aerosols at three rural/ remote locations in New York State were 1.0, 0.72, and 0.33 ng/m^3 (Dutkiewicz et al. 1987), and the enrichment over crustal abundance ranged from 920 to 1,650. The enrichment factor is smaller but similar to the mean enrichment factor of 1,880 for antimony in 29 cities (Gladney et al. 1984). The high enrichment indicates that the antimony is of anthropogenic origin. An analysis of the New York State data using backward-in-time air trajectories is consistent for the Midwest being the dominant source of antimony. An analysis of European sources and wind trajectories further illustrate that antimony may be transmitted over long distances. The average concentrations at a city in southern Norway were 0.54 ng/m^3 when the air masses came from the United Kingdom and 0.07 ng/m^3 when they came from over the Atlantic (Hillamo et al. 1988).

Twenty-four-hour samples collected at 10 locations in Washington, DC yielded average antimony concentrations ranging from 1.1 to 3.0 ng/m^3 (Kowalczyk et al. 1982). As a result of a chemical element balance analysis, the three major contributing sources in order of decreasing significance are believed to be refuse incineration, motor vehicles, and coal combustion. In a Houston study, the range of antimony concentrations in fine (0.1–2.5 µm) aerosols was 0–12 ng/m^3, whereas in particles >2.5 µm, the range was 0–4 ng/m^3 (Johnson et al. 1984). Median, mean, and maximum concentrations of antimony in aerosols at three sites in Quebec, Ontario, and Nova Scotia were 0.05–0.10, 0.11–0.23, and 0.37–2.17 ng/m^3,

respectively (Hopper and Barrie 1988). According to the Texas Air Control Board, the first- and second-highest annual average antimony concentrations in Texas between 1978 and 1982 were 452 and 50 ng/m^3 at Laredo and Dallas, respectively. The statewide 1978–1982 average was below the minimum detectible mean of 90 ng/m^3 (Wiersema et al. 1984).

Concentrations of antimony in 24-hour air samples at Kellogg, Idaho, an area with a large number of operating mines, ranged from 5.21 to 1,210 ng/m^3, with a mean of 146 ng/m^3 (Ragaini et al. 1977). The 6-month average concentration of antimony in air in an industrial area of England where a number of ferrous and nonferrous metal smelting and manufacturing works were concentrated was 40 ng/m^3. This is a factor of 50 higher than that found in rural areas (Pattenden et al. 1982). The maximum concentration at the industrial site was 69 ng/m^3.

The mean monthly concentration of antimony in precipitation at Birkenes in southern Norway ranged from 0.2 to 2.3 µg/L, with a mean of 0.6 µg/L (Pacyna et al. 1984). During the same period, the respective air concentrations were 0.19–0.80 and 0.43 ng/m^3. Rain samples were collected during two storms upwind and downwind of a copper smelter in Tacoma, Washington. Antimony in rainwater originated primarily from the smelter. The mean total antimony concentration in rainwater downwind from the smelter was 1.3 µg/L; the concentration upwind was 0.03 µg/L (Vong et al. 1988). Eighty percent of the antimony in rainwater was dissolved (i.e., passed through a 0.45-µm filter).

Antimony is almost entirely found in the particulate, as opposed to the dissolved fraction of snow (Landsberger et al. 1983). The antimony content of snow particulate matter in samples from Montreal, Canada, ranged from 4 to 145 ppm. Another sampling of snow around Montreal found total antimony concentrations of 1–8.7 ppb and enrichment factors of 39–590 (Zikovsky and Badillo 1987).

Antimony is a component of ammunition, and studies have been performed to ascertain the elemental concentrations of antimony in the air of indoor shooting ranges. Antimony might be expected in such situations because it is alloyed with lead in bullets, and lead stibnite and antimony sulfides are used as primers (Dams et al. 1988). After an intensive 3-hour shooting exercise, levels of antimony reached 119 µg/m^3 (190,000 ng/m^3), or 4 orders of magnitude over ambient levels (Vandecasteele et al. 1988). An instructor at the shooting range had a time-weighted average (TWA) inhalable antimony concentration of 12.0 µg/m^3 (1,200 ng/m^3) compared with the threshold limit value (TLV) of 500 µg/m^3 (500,000 ng/m^3). An American study conducted at the National Guard Armory in Washington, DC, during routine daytime and gun club use, found indoor antimony concentrations ranging from 57 to 216 µg/m^3 (57,000–

216,000 ng/m^3) versus background air ranging from 1.5 to 2.3 µg/m^3 (1,500–2,300 ng/m^3), an enrichment of 9,900 over District of Columbia air (Olmez et al. 1985). More than 60% of the antimony was associated with respirable particles with an aerodynamic diameter <3.5 pm (<3,500 ppb).

6.4.2 Water

The National Water-Quality Assessment (NAWQA) program surveyed groundwater across the United States from 1992 to 2003 and generally found low concentrations of antimony in the water. Median concentrations were reported as <1 µg/L (ppb) (USGS 2011). Other studies also reported low concentrations of antimony in water. Eckel and Jacob (1989) gathered water monitoring data from the Water Resources Division of the U.S. Geological Survey (USGS) covering the period from about 1960 to September, 1988, and found that all but 70 of 1,077 entries for dissolved antimony were below 5 µg/L. The geometric mean and standard deviation of the 70 values >5 µg/L were 12 and 1.93 µg/L, respectively. The concentrations of dissolved antimony were 1.62 nM (0.197 µg/L) in the St. Lawrence River at Massena, New York and 2.73 nM (0.332 µg/L) in the Yukon River. European rivers had dissolved antimony at concentrations ranging from <0.03 to 4.43 nM (0.004–0.539 µg/L) (Andreae and Froelich 1984).

Geothermal waters often have naturally elevated levels of trace metals such as arsenic, mercury, and antimony. The speciation of these compounds is complex and can change during sampling, storage, and analysis; therefore, results are usually reported as the total amount present in the geothermal water. Analysis of 268 thermal springs in Yellowstone National Park showed total antimony levels ranging from 9 to 166 µg/L for sampling conducted from 1966 to 1975 (Stauffer and Thompson 1984). USGS (2010) analyzed water samples from streams, tributaries, drainage channels, and other water bodies at 104 locations in the Yellowstone National Park, Wyoming from 2006 to 2008. The results of this study are summarized in Table 6-5.

These data are consistent with antimony levels in geothermal waters in other parts of the world. For example, antimony levels ranged from 0.05 to 244 µg/L (n=75), with a mean value of 35 µg/L for geothermal waters sampled in various locations of Japan.

Table 6-5. Total Antimony Levels in Water Samples Collected at Yellowstone National Park

Sampling location	Antimony (µg/L)
Norris-Mammoth Corridor and West Nymph Creek	<1–6
Norris Geyser Basin	<1–180
Gibbon Canyon and Geyser Springs Group	3–95
Crater Hills area	1–150
Ojo Caliente Spring and its discharge channel, Lower Geyser Basin	10–94
Porcupine Hills area	62–123
Midway Geyser Basin and the Rabbit Creek area	0–82
Mud Volcano area	<0.5–6
Washburn Hot Springs	<0.5

Source: USGS 2010

Anthropogenic activity can result in elevated levels of antimony in nearby water systems. A study in Luxembourg found higher concentrations of antimony in samples close to an ore site as compared to concentrations further from the site (Filella et al. 2009b). Similarly, a study in Corsica found higher levels of antimony in the water after crossing the mining soils, with concentrations decreasing further downstream (Migon and Mori 1999).

Sb(V) was the most prevalent species of antimony found in drinking water. Sb(V) is expected to predominate due to the oxidative treatments used in water disinfection processes (Belzile et al. 2011). Sb(V) was also the predominant species in oceans at mean concentrations of 200 ng/L. Sb(V) is predominant in oxic and mildly reducing environments. Sb(III) is predominant in anoxic waters and porewaters, and in reducing conditions. The presence of thermodynamically unfavorable Sb(III) in oxygenated surface waters has been attributed largely to phytoplankton activity (Chen et al. 2003).

The major antimony mining area in the United States was the Kellogg district in northern Idaho, and mining and smelting wastes have been dumped into the South Fork of the Coeur d'Alene River for over 80 years (Mok and Wai 1990). The South Fork joins with the North Fork of the river to form the Main Stem of the Coeur d'Alene River somewhat below Kellogg. Mean and maximum total dissolved antimony concentrations at two sites on the South Fork were 4.3 and 8.2 µg/L, respectively. Mean and maximum concentrations at six stations on the Main Stem ranged from 0.6 to 1.0 and from 0.8 to 1.9 µg/L, respectively. Those at a station on the unpolluted North Fork were 0.09 and 0.2 µg/L, respectively.

Since antimony is used in solder, there has been interest as to whether antimony will leach from pipes soldered with antimony-containing solder into drinking water. Leaching of antimony from tin/antimony (Sn/Sb) solder when it comes in contact with water with pH of 5.2–8.6 was evaluated using loops of pipe containing 20 solder joints (Murrell 1987). Antimony was undetectable (<4 ppb) in the water at first, but rose to 10 ppb after 4 days and 68 ppb (at pH 7.4) after 4 weeks. A study was conducted at the University of Washington to evaluate the potential for leaching of metals into drinking water from 95/5 Sn/Sb solder (Herrera et al. 1982). After a series of static and continuous-flow laboratory tests and evaluation of field samples from university buildings, it was concluded that increases in antimony concentration as a result of corrosion and leaching were minimal and would not contribute significantly to dietary antimony intake. Only one of the field samples of standing water from university buildings containing Sn/Sb solder joints was above the detection limit of 0.6 ppb. The sample contained 2 ppb of antimony, one-half of which

was dissolved. Examination of the solder joints indicated that a double passivation film of tin monoxide (SnO) and tin dioxide (SnO_2) forms and inhibits leaching.

6.4.3 Sediment and Soil

Antimony is naturally present in the earth's crust at levels of about 0.2–0.3 µg/g (ppm), but these levels vary by location (Telford et al. 2008). A survey of soils throughout the conterminous United States conducted by the USGS showed that antimony concentrations ranged from <1 to 8.8 ppm (µg/g) with an average concentration of 0.48 ppm (µg/g). This was the third lowest concentration of the 50 elements surveyed (Shacklette and Boerngen 1984). In this survey, samples were taken at a depth of 20 cm at 1,318 sampling sites. Soils not derived from ore-bearing rock or close to industrial sources do not generally contain more than 1 ppm (µg/g) of antimony. Background concentrations for antimony in soil ranged from 0.06 to 0.79 µg/g in seven Florida soil orders. Concentrations were dependent on the location, mineralization, parent material differences, varying degrees of anthropogenic influence, and different sampling strategies (Wilson et al. 2010). Elevated levels of antimony in soil samples are commonly associated with anthropogenic activities such as mining, fossil fuel combustion, smelting, and other activities. Samples of soil were collected from the decommissioned Hanford Site along the Columbia River in 2008. The Hanford site was utilized to produce plutonium. Antimony was detected in 27 out of 158 samples at a mean concentration of 0.113 µg/g. Antimony and selenium were not able to be detected in the majority of the samples (DOE 2009b). The distribution of antimony at two sites in Austria, with close proximity to traffic routes, was evaluated by Amereih et al. (2005) at two sampling depths (0–5 and 5–10 cm from the soil surface) and three distances (0.2, 2, and 10 m) from the edge of the road. In addition to roadside soil, samples were also obtained from Lungau, an alpine region with negligible traffic. Table 6-6 summarizes the results from this study during two sampling periods (2002 and 2005).

Examining the monitoring data from this study shows clear trends in the antimony levels in the soils reflective of anthropogenic contributions due to the presence of motor vehicles at the Knittelfeld and Rankweil locations as compared to the site with negligible vehicular traffic. Moreover, greater antimony levels are observed at both sampling depths the nearer to the road the soil samples were obtained (0.2 versus 2 versus 10 m). Levels of antimony decreased to near background levels within a few meters from the edge of the road.

Table 6-6. Antimony Levels at Three Locations With Different Vehicular Traffic

Location[a]	Distance from road (m)	Sample depth (cm)	Total Sb µg/g (2002)	Total Sb µg/g (2005)
Lungau	Not applicable	0–5	0.64	Not available
Lungau	Not applicable	5–10	0.81	Not available
Knittelfeld	0.2	0–5	6.30	8.68
Knittelfeld	0.2	5–10	3.80	4.78
Knittelfeld	2	0–5	1.75	1.99
Knittelfeld	2	5–10	1.51	1.96
Knittelfeld	10	0–5	1.21	1.16
Knittelfeld	10	5–10	1.13	1.13
Rankweil	0.2	0–5	2.74	Not available
Rankweil	0.2	5–10	1.83	Not available
Rankweil	2	0–5	1.52	Not available
Rankweil	2	5–10	1.21	Not available
Rankweil	10	0–5	0.91	Not available
Rankweil	10	5–10	0.82	Not available

[a]Vehicular traffic at the Knittelfeld and Rankweil sampling locations exceeds 20,000 vehicles per day, while there is no vehicular traffic at the Lungau location.

Source: Amereih et al. 2005

High concentrations of antimony were observed in soil at a shooting range. Antimony concentrations (only Sb(V)) were 4,000 µg/g in soil samples collected at a depth of 1 cm, 1,600–17,500 µg/g in soil samples collected at 0–5 cm, 3,400 mg/kg at 5–15 cm, 1,300 µg/g at 16 cm, and 8,600 µg/g at 25–45 cm at different sites at the shooting range (Scheinost et al. 2006).

Levels of mean antimony, Sb(III), and Sb(V) in contaminated soils from the Hillgrove mine located in New South Wales, Australia were measured in six samples. This facility mines for gold and antimony and has been in operation for over 100 years. There were higher levels of Sb(V) than Sb(III) in the soil samples, ranging from 12 to 27 µg/g for Sb(III) and from 211 to 384 µg/g for Sb(V). Total mean antimony levels ranged from 470 to 849 µg/g (Telford et al. 2008). Concentrations of antimony were also high in the sediment around mining sites in Corsica. The levels of antimony decreased with increasing distance downstream from the site. Concentrations ranged from 8 to 1,108 µg/g in January 1993 and from 10 to 1,005 µg/g in March 1993 depending upon the sampling location (Migon and Mori 1999). The greatest concentrations occurred at a sampling location on the Presa River nearby the mine and gradually decreased at sampling locations 10 km away where the Presa River runs into the Bravona River.

Levels of Sb(III), Sb(V), and total antimony were monitored at three locations in sediment from the Plawniowice reservoir in Poland nearby metallurgy and coal mining operations (Jablonska-Czapla et al. 2014). Levels of Sb(III) varied between approximately 20–45 µg/g in the upper (0–5 cm) sediment profile and approximately 20–35 µg/g in sediment collected from a depth of 15–20 cm. Sb(V) levels were similar in both the upper sediment samples and the lower sediment samples with levels ranging from approximately 5 to 25 µg/g.

6.4.4 Other Environmental Media

Antimony trioxide (Sb_2O_3) is used in the production of PET. The antimony content in PET has been reported to be as high as 190–300 mg/kg. Leaching of antimony into PET water bottles has been reported. European PET bottled water contained 359 ng/L of antimony; however, the low-density PET from the same brand had 3.9 ng/L of antimony. Increased temperature and length of time stored may contribute to more antimony being released into the bottles. Levels of antimony increased from 200 to 7,800–9,700 ng/L in heated water bottles (at 80°C for 48 hours). Heated PET packing materials had antimony concentrations ranging from 50 to 285 mg/kg and non-heated containers had levels <0.1–24 µg/kg. Concentrations of antimony in food has been reported to be <1.0 µg/g (Belzile et al. 2011).

Antimony has been detected in commercial juices. Juices of blackcurrant, mixed fruit, strawberry, raspberry, sour cherry, mint, and synthetic caramel purchased from Greece, Denmark, and Scotland were analyzed for antimony content. The highest concentration of antimony from the 42 samples was 13.6 µg/L, reported in sour cherry juice packaged in glass (Hansen et al. 2010).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population may be exposed to antimony through ingestion of food and drinking water, inhalation of particulates from ambient air, or ingestion of contaminated soil or dust. Occupational exposures of antimony may occur at smelters, coal-fired plants, and refuse incinerators that process or release antimony. Dermal exposure may occur through skin contact with soil, water, or other substances containing antimony. Absorption, distribution, and excretion of antimony are variable based on oxidation state. Urinary excretion appears to be greater for Sb(V) than for Sb(III) compounds (Elinder and Friberg, 1986).

In the Fourth National Report on Human Exposures to Environmental Chemicals reported by the Centers for Disease Control and Prevention (CDC 2015) results from the NHANES updated tables 1999–2012 were provided for antimony. Antimony levels in urine (see Table 6-7), and urine (creatinine corrected) (see Table 6-8) were evaluated for a variety of age groups and ethnicities. Recent exposure to antimony is reflected in urinary samples (CDC 2015). The geometric mean and median concentrations of urinary antimony have decreased over time, which may be due to decreases in exposure or methodological differences.

Gebel et al. (1998b) investigated urine, blood, and scalp hair for antimony biomonitoring. No association between elevated soil levels and urinary antimony levels were found in this study of >200 German residents. A high proportion of blood samples were below the limit of detection. Antimony was detected in hair samples from individuals in Rio de Janeiro at concentrations that ranged from <0.03 to <1.8 µg/g. The samples were for both men and women and were collected from the scalp in the occipital area (back of the head) (Miekeley et al. 1998). In an analogous study, the mean concentration of antimony in hair samples from 55 men and women from Scranton, Pennsylvania contained 0.096 ppm of antimony. The hair samples of populations from cities in four other countries contained mean antimony levels between 0.11 and 0.86 ppm (Takagi et al. 1986). A Japanese national study analyzing antimony concentrations in

Table 6-7. Geometric Mean and Selected Percentiles of Urinary Antimony (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	0.132 (0.120–0.145)	0.130 (0.120–0.150)	0.220 (0.200–0.230)	0.330 (0.300–0.350)	0.430 (0.390–0.470)	2,276
	2001–2002	0.134 (0.126–0.142)	0.130 (0.130–0.140)	0.190 (0.180–0.200)	0.270 (0.250–0.310)	0.350 (0.320–0.400)	2,690
	2003–2004	*	0.080 (<LOD–0.090)	0.130 (0.120–0.150)	0.200 (0.190–0.220)	0.280 (0.250–0.320)	2,558
	2005–2006	0.073 (0.066–0.081)	0.070 (0.070–0.080)	0.120 (0.110–0.140)	0.220 (0.180–0.250)	0.300 (0.270–0.360)	2,576
	2007–2008	0.061 (0.057–0.066)	0.060 (0.060–0.060)	0.100 (0.090–0.110)	0.170 (0.140–0.200)	0.240 (0.220–0.260)	2,627
	2009–2010	0.056 (0.053–0.059)	0.050 (0.050–0.060)	0.090 (0.090–0.100)	0.170 (0.140–0.180)	0.230 (0.200–0.280)	2,847
	2011–2012	*	0.047 (0.042–0.052)	0.083 (0.075–0.091)	0.144 (0.125–0.158)	0.188 (0.169–0.222)	2,504
Age group							
6–11 years	1999–2000	0.176 (0.154–0.200)	0.190 (0.160–0.210)	0.260 (0.230–0.280)	0.350 (0.300–0.400)	0.440 (0.320–0.600)	316
	2001–2002	0.146 (0.134–0.160)	0.150 (0.130–0.160)	0.200 (0.180–0.210)	0.270 (0.240–0.330)	0.340 (0.280–0.440)	368
	2003–2004	0.099 (0.087–0.114)	0.100 (0.070–0.120)	0.160 (0.120–0.200)	0.240 (0.190–0.310)	0.310 (0.230–0.330)	290
	2005–2006	0.075 (0.063–0.088)	0.080 (0.060–0.090)	0.110 (0.090–0.130)	0.190 (0.120–0.260)	0.240 (0.170–0.340)	355
	2007–2008	0.068 (0.061–0.077)	0.070 (0.060–0.080)	0.110 (0.090–0.130)	0.170 (0.150–0.210)	0.230 (0.180–0.280)	394
	2009–2010	0.069 (0.061–0.079)	0.070 (0.060–0.080)	0.120 (0.100–0.150)	0.220 (0.150–0.260)	0.260 (0.230–0.350)	378
	2011–2012	0.064 (0.059–0.069)	0.059 (0.049–0.072)	0.108 (0.094–0.124)	0.169 (0.152–0.188)	0.206 (0.182–0.257)	399
12–19 years	1999–2000	0.158 (0.141–0.178)	0.170 (0.150–0.180)	0.240 (0.210–0.270)	0.350 (0.290–0.420)	0.460 (0.350–0.510)	663
	2001–2002	0.169 (0.156–0.184)	0.160 (0.150–0.180)	0.240 (0.220–0.260)	0.350 (0.320–0.410)	0.460 (0.400–0.500)	762
	2003–2004	0.105 (0.095–0.115)	0.100 (0.090–0.120)	0.150 (0.140–0.160)	0.230 (0.200–0.270)	0.290 (0.250–0.370)	725
	2005–2006	0.092 (0.083–0.101)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.240 (0.200–0.270)	0.280 (0.250–0.320)	701
	2007–2008	0.079 (0.069–0.091)	0.080 (0.070–0.090)	0.130 (0.110–0.140)	0.210 (0.150–0.230)	0.230 (0.210–0.340)	376
	2009–2010	0.063 (0.056–0.071)	0.060 (0.050–0.070)	0.100 (0.090–0.120)	0.180 (0.150–0.210)	0.270 (0.180–0.370)	451
	2011–2012	0.065 (0.057–0.073)	0.065 (0.048–0.081)	0.106 (0.098–0.126)	0.173 (0.137–0.202)	0.218 (0.166–0.283)	390
≥20 years	1999–2000	0.123 (0.112–0.137)	0.120 (0.110–0.130)	0.200 (0.180–0.220)	0.310 (0.290–0.350)	0.430 (0.390–0.470)	1,297
	2001–2002	0.128 (0.119–0.136)	0.130 (0.120–0.130)	0.180 (0.170–0.190)	0.250 (0.220–0.300)	0.330 (0.280–0.390)	1,560
	2003–2004	*	0.070 (<LOD–0.080)	0.120 (0.100–0.140)	0.190 (0.170–0.210)	0.270 (0.220–0.320)	1,543
	2005–2006	0.070 (0.064–0.078)	0.070 (0.060–0.080)	0.120 (0.110–0.140)	0.220 (0.180–0.270)	0.320 (0.260–0.420)	1,520
	2007–2008	0.058 (0.054–0.062)	0.060 (0.050–0.060)	0.090 (0.090–0.100)	0.160 (0.130–0.190)	0.240 (0.210–0.270)	1,857
	2009–2010	0.054 (0.051–0.057)	0.050 (0.050–0.050)	0.090 (0.080–0.090)	0.150 (0.140–0.180)	0.220 (0.190–0.270)	2,018
	2011–2012	*	0.044 (<LOD–0.051)	0.076 (0.066–0.087)	0.129 (0.112–0.152)	0.171 (0.158–0.228)	1,715

Table 6-7. Geometric Mean and Selected Percentiles of Urinary Antimony (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI) 50th	75th	90th	95th	Sample size
Gender							
Males	1999–2000	0.143 (0.131–0.157)	0.150 (0.130–0.160)	0.240 (0.220–0.260)	0.350 (0.330–0.390)	0.470 (0.390–0.570)	1,132
	2001–2002	0.145 (0.136–0.154)	0.140 (0.130–0.150)	0.200 (0.190–0.210)	0.310 (0.280–0.330)	0.390 (0.350–0.440)	1,335
	2003–2004	0.095 (0.088–0.103)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.220 (0.200–0.250)	0.320 (0.270–0.350)	1,281
	2005–2006	0.085 (0.076–0.095)	0.080 (0.080–0.090)	0.140 (0.120–0.160)	0.250 (0.210–0.290)	0.350 (0.260–0.460)	1,271
	2007–2008	0.068 (0.062–0.076)	0.070 (0.060–0.070)	0.110 (0.100–0.120)	0.210 (0.170–0.230)	0.280 (0.230–0.340)	1,327
	2009–2010	0.060 (0.055–0.065)	0.060 (0.050–0.070)	0.100 (0.090–0.110)	0.170 (0.150–0.200)	0.250 (0.200–0.290)	1,397
	2011–2012	0.057 (0.052–0.063)	0.052 (0.044–0.061)	0.089 (0.080–0.100)	0.152 (0.124–0.169)	0.196 (0.169–0.259)	1,262
Females	1999–2000	0.122 (0.109–0.137)	0.120 (0.110–0.140)	0.200 (0.180–0.220)	0.300 (0.280–0.340)	0.400 (0.350–0.460)	1,144
	2001–2002	0.125 (0.117–0.133)	0.120 (0.120–0.130)	0.180 (0.160–0.190)	0.240 (0.220–0.280)	0.320 (0.260–0.360)	1,355
	2003–2004	*	< LOD	0.120 (0.090–0.140)	0.180 (0.150–0.220)	0.230 (0.190–0.330)	1,277
	2005–2006	0.063 (0.057–0.071)	0.060 (0.050–0.070)	0.100 (0.090–0.120)	0.180 (0.150–0.230)	0.270 (0.200–0.330)	1,305
	2007–2008	0.055 (0.052–0.058)	0.050 (0.050–0.060)	0.090 (0.080–0.100)	0.130 (0.120–0.150)	0.200 (0.170–0.230)	1,300
	2009–2010	0.052 (0.049–0.056)	0.050 (0.040–0.050)	0.090 (0.080–0.090)	0.150 (0.130–0.170)	0.220 (0.190–0.270)	1,450
	2011–2012	*	0.043 (<LOD–0.049)	0.074 (0.068–0.082)	0.131 (0.122–0.149)	0.182 (0.166–0.218)	1,242
Race/ethnicity							
Mexican Americans	1999–2000	0.132 (0.108–0.161)	0.140 (0.120–0.170)	0.210 (0.180–0.240)	0.300 (0.260–0.390)	0.430 (0.330–0.560)	787
	2001–2002	0.142 (0.130–0.154)	0.130 (0.130–0.150)	0.200 (0.170–0.230)	0.260 (0.240–0.320)	0.360 (0.300–0.400)	683
	2003–2004	0.093 (0.079–0.110)	0.090 (<LOD–0.120)	0.140 (0.120–0.160)	0.190 (0.160–0.260)	0.270 (0.210–0.330)	618
	2005–2006	0.093 (0.082–0.105)	0.090 (0.080–0.100)	0.150 (0.140–0.170)	0.250 (0.210–0.340)	0.470 (0.270–0.850)	652
	2007–2008	0.069 (0.060–0.079)	0.070 (0.060–0.080)	0.110 (0.100–0.120)	0.190 (0.150–0.250)	0.270 (0.220–0.390)	515
	2009–2010	0.063 (0.060–0.067)	0.060 (0.060–0.070)	0.110 (0.090–0.120)	0.170 (0.150–0.200)	0.250 (0.200–0.270)	613
	2011–2012	0.056 (0.051–0.062)	0.053 (0.044–0.062)	0.086 (0.075–0.091)	0.134 (0.110–0.164)	0.174 (0.149–0.261)	317
Non-Hispanic blacks	1999–2000	0.175 (0.148–0.207)	0.180 (0.150–0.200)	0.260 (0.230–0.300)	0.400 (0.310–0.490)	0.490 (0.410–0.710)	554
	2001–2002	0.180 (0.164–0.197)	0.170 (0.160–0.190)	0.250 (0.220–0.280)	0.360 (0.320–0.410)	0.460 (0.370–0.530)	667
	2003–2004	0.108 (0.098–0.119)	0.110 (0.100–0.120)	0.160 (0.150–0.190)	0.230 (0.200–0.280)	0.310 (0.250–0.360)	723
	2005–2006	0.088 (0.077–0.100)	0.090 (0.080–0.100)	0.140 (0.130–0.170)	0.210 (0.190–0.250)	0.280 (0.240–0.320)	692
	2007–2008	0.085 (0.079–0.092)	0.080 (0.080–0.090)	0.130 (0.120–0.140)	0.210 (0.180–0.250)	0.290 (0.250–0.370)	589
	2009–2010	0.073 (0.065–0.081)	0.070 (0.060–0.080)	0.120 (0.110–0.140)	0.190 (0.160–0.250)	0.280 (0.220–0.350)	544
	2011–2012	0.070 (0.063–0.079)	0.068 (0.062–0.074)	0.110 (0.096–0.125)	0.182 (0.148–0.229)	0.254 (0.200–0.354)	669

Table 6-7. Geometric Mean and Selected Percentiles of Urinary Antimony (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	1999–2000	0.128 (0.115–0.144)	0.130 (0.110–0.140)	0.210 (0.190–0.230)	0.330 (0.280–0.350)	0.400 (0.360–0.500)	768
	2001–2002	0.126 (0.117–0.135)	0.130 (0.120–0.130)	0.180 (0.170–0.190)	0.250 (0.230–0.300)	0.340 (0.310–0.390)	1,132
	2003–2004	*	0.070 (<LOD–0.080)	0.130 (0.110–0.140)	0.190 (0.170–0.210)	0.280 (0.230–0.320)	1,074
	2005–2006	0.069 (0.062–0.077)	0.070 (0.060–0.080)	0.110 (0.100–0.130)	0.210 (0.170–0.260)	0.300 (0.240–0.380)	1,041
	2007–2008	0.057 (0.052–0.063)	0.060 (0.050–0.060)	0.090 (0.080–0.110)	0.150 (0.130–0.200)	0.230 (0.190–0.260)	1,095
	2009–2010	0.053 (0.050–0.057)	0.050 (0.040–0.050)	0.090 (0.080–0.090)	0.160 (0.130–0.190)	0.230 (0.190–0.280)	1,225
	2011–2012	*	0.044 (<LOD–0.049)	0.081 (0.069–0.095)	0.143 (0.118–0.159)	0.180 (0.159–0.231)	820
All Hispanics	2011–2012	*	0.046 (<LOD–0.053)	0.079 (0.066–0.088)	0.128 (0.110–0.149)	0.174 (0.149–0.208)	573
Asians	2011–2012	*	<LOD	0.066 (0.054–0.075)	0.103 (0.075–0.145)	0.145 (0.100–0.194)	353

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

Table 6-8. Geometric Mean and Selected Percentiles of Urinary Antimony (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000	0.124 (0.108–0.143)	0.119 (0.102–0.143)	0.185 (0.164–0.214)	0.276 (0.233–0.333)	0.385 (0.333–0.430)	2,276
	2001–2002	0.126 (0.119–0.134)	0.120 (0.115–0.126)	0.173 (0.162–0.188)	0.267 (0.242–0.300)	0.364 (0.320–0.414)	2,689
	2003–2004	*	0.080 (<LOD–0.086)	0.135 (0.119–0.143)	0.208 (0.192–0.230)	0.277 (0.250–0.294)	2,558
	2005–2006	0.072 (0.068–0.077)	0.070 (0.060–0.070)	0.100 (0.100–0.110)	0.160 (0.150–0.190)	0.230 (0.190–0.290)	2,576
	2007–2008	0.064 (0.060–0.068)	0.060 (0.060–0.060)	0.090 (0.080–0.100)	0.140 (0.140–0.160)	0.200 (0.170–0.230)	2,627
	2009–2010	0.060 (0.056–0.064)	0.060 (0.050–0.060)	0.090 (0.080–0.090)	0.140 (0.120–0.160)	0.200 (0.180–0.230)	2,847
	2011–2012	*	0.059 (0.055–0.063)	0.092 (0.085–0.100)	0.152 (0.135–0.171)	0.223 (0.181–0.261)	2,502
Age group							
6–11 years	1999–2000	0.191 (0.147–0.248)	0.185 (0.156–0.220)	0.250 (0.200–0.417)	0.447 (0.271–0.741)	0.741 (0.333–10.30)	316
	2001–2002	0.178 (0.159–0.200)	0.173 (0.150–0.193)	0.228 (0.200–0.272)	0.338 (0.265–0.480)	0.471 (0.313–0.727)	368
	2003–2004	0.116 (0.103–0.130)	0.118 (0.098–0.136)	0.167 (0.146–0.187)	0.256 (0.194–0.317)	0.333 (0.250–0.500)	290
	2005–2006	0.092 (0.081–0.104)	0.090 (0.080–0.110)	0.130 (0.110–0.150)	0.180 (0.150–0.210)	0.220 (0.180–0.270)	355
	2007–2008	0.089 (0.079–0.100)	0.090 (0.070–0.100)	0.120 (0.110–0.140)	0.200 (0.150–0.240)	0.300 (0.200–0.370)	394
	2009–2010	0.094 (0.084–0.106)	0.090 (0.080–0.100)	0.140 (0.120–0.160)	0.200 (0.170–0.250)	0.280 (0.220–0.320)	378
	2011–2012	0.091 (0.081–0.102)	0.091 (0.078–0.100)	0.130 (0.116–0.147)	0.206 (0.153–0.283)	0.308 (0.218–0.340)	398
12–19 years	1999–2000	0.121 (0.104–0.140)	0.120 (0.095–0.146)	0.176 (0.146–0.207)	0.259 (0.206–0.310)	0.310 (0.228–0.421)	663
	2001–2002	0.121 (0.112–0.131)	0.115 (0.106–0.127)	0.160 (0.138–0.186)	0.224 (0.199–0.245)	0.266 (0.244–0.310)	762
	2003–2004	0.075 (0.068–0.082)	0.068 (0.061–0.077)	0.100 (0.092–0.113)	0.156 (0.126–0.173)	0.193 (0.172–0.255)	725
	2005–2006	0.070 (0.065–0.076)	0.070 (0.060–0.080)	0.100 (0.090–0.110)	0.140 (0.120–0.150)	0.170 (0.150–0.250)	701
	2007–2008	0.062 (0.054–0.070)	0.060 (0.050–0.070)	0.090 (0.070–0.100)	0.120 (0.100–0.160)	0.160 (0.110–0.240)	376
	2009–2010	0.059 (0.053–0.066)	0.060 (0.050–0.060)	0.090 (0.070–0.100)	0.130 (0.110–0.170)	0.180 (0.150–0.220)	451
	2011–2012	0.062 (0.055–0.069)	0.058 (0.051–0.067)	0.085 (0.070–0.106)	0.147 (0.115–0.181)	0.222 (0.122–0.373)	390
≥20 years	1999–2000	0.118 (0.104–0.135)	0.111 (0.097–0.135)	0.175 (0.149–0.209)	0.263 (0.227–0.320)	0.352 (0.320–0.391)	1,297
	2001–2002	0.122 (0.115–0.129)	0.115 (0.108–0.121)	0.167 (0.153–0.181)	0.265 (0.241–0.300)	0.364 (0.318–0.405)	1,559
	2003–2004	*	0.079 (<LOD–0.087)	0.135 (0.116–0.145)	0.209 (0.195–0.233)	0.278 (0.250–0.294)	1,543
	2005–2006	0.070 (0.066–0.075)	0.060 (0.060–0.070)	0.100 (0.090–0.110)	0.170 (0.150–0.190)	0.250 (0.190–0.300)	1,520
	2007–2008	0.062 (0.058–0.066)	0.060 (0.050–0.060)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.200 (0.160–0.240)	1,857
	2009–2010	0.057 (0.053–0.061)	0.050 (0.050–0.060)	0.080 (0.080–0.090)	0.130 (0.120–0.140)	0.190 (0.160–0.220)	2,018
	2011–2012	*	0.056 (<LOD–0.060)	0.088 (0.078–0.097)	0.145 (0.127–0.171)	0.215 (0.179–0.240)	1,714

Table 6-8. Geometric Mean and Selected Percentiles of Urinary Antimony (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Gender							
Males	1999–2000	0.112 (0.099–0.127)	0.109 (0.095–0.127)	0.164 (0.146–0.181)	0.226 (0.204–0.268)	0.320 (0.235–0.391)	1,132
	2001–2002	0.114 (0.107–0.123)	0.108 (0.103–0.115)	0.153 (0.138–0.171)	0.228 (0.205–0.250)	0.333 (0.281–0.438)	1,334
	2003–2004	0.080 (0.076–0.084)	0.075 (0.069–0.081)	0.122 (0.111–0.132)	0.192 (0.173–0.209)	0.253 (0.230–0.278)	1,281
	2005–2006	0.070 (0.064–0.077)	0.060 (0.060–0.070)	0.100 (0.090–0.120)	0.160 (0.130–0.220)	0.250 (0.170–0.310)	1,271
	2007–2008	0.061 (0.057–0.066)	0.060 (0.050–0.060)	0.090 (0.080–0.100)	0.140 (0.130–0.160)	0.210 (0.160–0.260)	1,327
	2009–2010	0.055 (0.050–0.060)	0.050 (0.050–0.060)	0.080 (0.070–0.100)	0.130 (0.120–0.150)	0.190 (0.160–0.210)	1,397
	2011–2012	0.054 (0.050–0.058)	0.051 (0.048–0.057)	0.078 (0.071–0.089)	0.132 (0.120–0.151)	0.186 (0.161–0.224)	1,261
Females	1999–2000	0.137 (0.117–0.161)	0.131 (0.108–0.164)	0.213 (0.176–0.247)	0.320 (0.263–0.417)	0.429 (0.357–0.485)	1,144
	2001–2002	0.139 (0.131–0.148)	0.132 (0.124–0.140)	0.196 (0.178–0.211)	0.295 (0.267–0.317)	0.371 (0.333–0.444)	1,355
	2003–2004	*	<LOD	0.143 (0.125–0.161)	0.225 (0.188–0.261)	0.288 (0.250–0.333)	1,277
	2005–2006	0.074 (0.070–0.078)	0.070 (0.070–0.070)	0.110 (0.100–0.110)	0.170 (0.150–0.190)	0.220 (0.180–0.300)	1,305
	2007–2008	0.067 (0.062–0.071)	0.060 (0.060–0.070)	0.100 (0.090–0.100)	0.140 (0.130–0.160)	0.200 (0.160–0.230)	1,300
	2009–2010	0.064 (0.060–0.069)	0.060 (0.060–0.070)	0.090 (0.090–0.100)	0.150 (0.130–0.170)	0.220 (0.180–0.260)	1,450
	2011–2012	*	0.066 (<LOD–0.071)	0.104 (0.094–0.112)	0.165 (0.145–0.193)	0.226 (0.183–0.303)	1,241
Race/ethnicity							
Mexican Americans	1999–2000	0.120 (0.107–0.135)	0.114 (0.105–0.129)	0.167 (0.148–0.203)	0.250 (0.209–0.315)	0.333 (0.280–0.357)	787
	2001–2002	0.138 (0.128–0.149)	0.130 (0.117–0.143)	0.182 (0.159–0.203)	0.269 (0.229–0.308)	0.338 (0.308–0.429)	682
	2003–2004	0.086 (0.076–0.098)	0.082 (<LOD–0.092)	0.129 (0.107–0.151)	0.189 (0.154–0.238)	0.238 (0.185–0.321)	618
	2005–2006	0.087 (0.076–0.099)	0.080 (0.070–0.080)	0.120 (0.110–0.130)	0.190 (0.150–0.310)	0.370 (0.200–0.800)	652
	2007–2008	0.069 (0.059–0.081)	0.060 (0.050–0.080)	0.100 (0.080–0.120)	0.160 (0.130–0.180)	0.200 (0.160–0.360)	515
	2009–2010	0.066 (0.063–0.071)	0.060 (0.060–0.060)	0.100 (0.080–0.110)	0.160 (0.130–0.190)	0.240 (0.190–0.280)	613
	2011–2012	0.063 (0.059–0.067)	0.061 (0.057–0.064)	0.089 (0.079–0.100)	0.133 (0.121–0.153)	0.183 (0.150–0.246)	317
Non-Hispanic blacks	1999–2000	0.114 (0.099–0.133)	0.112 (0.098–0.130)	0.163 (0.144–0.183)	0.236 (0.195–0.338)	0.343 (0.255–0.425)	554
	2001–2002	0.123 (0.113–0.134)	0.115 (0.106–0.127)	0.163 (0.150–0.181)	0.233 (0.208–0.267)	0.300 (0.248–0.373)	667
	2003–2004	0.078 (0.071–0.085)	0.074 (0.069–0.082)	0.109 (0.096–0.124)	0.170 (0.148–0.192)	0.222 (0.179–0.257)	723
	2005–2006	0.064 (0.058–0.071)	0.060 (0.050–0.070)	0.090 (0.080–0.090)	0.130 (0.120–0.150)	0.190 (0.150–0.220)	692
	2007–2008	0.062 (0.059–0.066)	0.060 (0.050–0.070)	0.090 (0.080–0.090)	0.140 (0.120–0.160)	0.180 (0.160–0.220)	589
	2009–2010	0.058 (0.053–0.063)	0.060 (0.050–0.060)	0.080 (0.070–0.090)	0.130 (0.110–0.160)	0.170 (0.150–0.190)	544
	2011–2012	0.055 (0.049–0.060)	0.052 (0.047–0.058)	0.077 (0.069–0.088)	0.121 (0.104–0.147)	0.175 (0.140–0.232)	669

Table 6-8. Geometric Mean and Selected Percentiles of Urinary Antimony (Creatinine Corrected) (in µg/g of Creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES)

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Non-Hispanic whites	1999–2000	0.129 (0.109–0.152)	0.125 (0.102–0.152)	0.195 (0.167–0.225)	0.298 (0.239–0.352)	0.400 (0.333–0.444)	768
	2001–2002	0.127 (0.117–0.138)	0.120 (0.113–0.130)	0.176 (0.159–0.198)	0.280 (0.241–0.317)	0.380 (0.318–0.471)	1,132
	2003–2004	*	0.081 (<LOD–0.089)	0.139 (0.124–0.147)	0.217 (0.200–0.238)	0.286 (0.253–0.333)	1,074
	2005–2006	0.072 (0.068–0.077)	0.070 (0.060–0.070)	0.110 (0.100–0.110)	0.170 (0.150–0.190)	0.230 (0.190–0.280)	1,041
	2007–2008	0.064 (0.060–0.069)	0.060 (0.050–0.070)	0.090 (0.080–0.100)	0.140 (0.140–0.160)	0.210 (0.170–0.230)	1,095
	2009–2010	0.060 (0.055–0.065)	0.060 (0.050–0.060)	0.090 (0.080–0.100)	0.140 (0.120–0.170)	0.200 (0.170–0.250)	1,225
	2011–2012	*	0.060 (<LOD–0.067)	0.097 (0.088–0.108)	0.161 (0.135–0.183)	0.224 (0.181–0.273)	818
All Hispanics	2011–2012	*	0.058 (<LOD–0.065)	0.085 (0.073–0.097)	0.132 (0.113–0.161)	0.181 (0.153–0.214)	573
Asians	2011–2012	*	<LOD	0.087 (0.072–0.107)	0.153 (0.132–0.177)	0.215 (0.171–0.290)	353

<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
*Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CI = confidence interval

Source: CDC 2015

washed hair samples from 234 healthy individuals reported a geometric mean concentration and standard deviation of 0.078 and 2.5 ppm, respectively. No significant differences between different sexes or age groups were noted (Ohmori et al. 1981).

In another Japanese study, hair and nail samples taken from workers at an antimony refinery, nearby residents, and a control group were analyzed before and after washing with a nonionic, surface-active agent in an ultrasonic cleaner (Katayama and Ishide 1987). The respective concentrations of antimony in the nails of the three groups were 730, 2.46, and 0.19 ppm before washing and 230, 0.63, and 0.09 ppm after washing. The concentrations of antimony in the hair of workers before and after washing were 222 and 196 ppm, respectively. The concentrations of antimony in the hair of control subjects before and after washing were 0.21 and 0.15 ppm, respectively. Nail samples from 71 Americans contained an average of 0.41 ppm of antimony. Averages for residents of four other countries ranged from 0.28 to 0.70 ppm (Takagi et al. 1988).

Elevated urinary antimony levels were reported in workers exposed to airborne antimony (Bailly et al. 1991; Iavicoli et al. 2002; Kentner et al. 1995; Liao et al. 2004; Ludersdorf et al. 1987). A National Occupational Exposure Survey (NOES) conducted by NIOSH from 1981 to 1983 estimated that 373,460 workers were potentially exposed to antimony (molecular formula unknown) in the United States in 1981–1983 (NIOSH 1989). An estimated 226,645 workers were exposed to antimony trioxide, antimony sulfide, antimony oxide, antimony pentoxide, antimony dialkyldithiocarbamate, and other antimony compounds. The total estimated number of workers exposed to antimony and all of its compounds was 486,347. These estimates are preliminary since all of the data for trade-name products that may contain antimony were not analyzed. The NOES was based on field surveys of 4,490 facilities. It was designed as a nationwide survey based on a statistical sample of virtually all workplace environments in the United States where eight or more persons are employed in all standard industrial codes (SIC) except mining and agriculture. The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide only estimates of the number of workers potentially exposed to chemicals in the workplace. EPA states that the NOES figures substantially overestimate occupational exposure to antimony and compounds (EPA 1983a).

Reported levels of antimony were high in occupationally exposed individuals compared to levels in the urine of control subjects ranging from 0.18–2.16 µg/L. Levels ranged from 0.08 to 32.6 µg/L in the urine of refinery workers, from 0.1 to 36.1 µg/L in chemical manufacturers, and from 1.5 to 149.2 µg/L in

battery manufacturers. The authors specified that the levels of antimony were 5 times higher from battery workers than other workers. Battery manufacturers were likely exposed to stibine (SbH_3) during the charging process of batteries (Smith et al. 1995).

Concentrations of antimony were examined in the urine of workers at the Punchancavi site in Chile. Concentrations of total antimony and Sb(V) were 6–6.3 and 2.4–6.2 µg/L, respectively. Urine sample analysis determined that most samples had concentrations of total antimony and Sb(V) that were below the limit of detection. No Sb(III) was found in the samples (Quiroz et al. 2011).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.8, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume than adults. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

The NHANES 1999–2012 reported antimony levels in urine (see Tables 6-7 and 6-8) for children in different age groups (CDC 2015). Infant urinary antimony levels reported in the scientific literature are similar to those reported for young children in Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2009). Antimony levels >1 µg/L were found in 4% of 126 term infants; 7% had levels <0.02 µg/L and 90.5% had levels <0.5 µg/L (Dezateux et al. 1997). Higher levels of antimony were found in postmortem liver and serum samples from infants who died as a result of sudden infant death syndrome (Cullen et al. 1998; Jenkins et al. 1998). Mean serum antimony concentrations ranged from 0.16 to 0.18 µg/L for 100 healthy infants, 2–56 weeks old. Urinary antimony concentrations were not detected in 5% of the infants, median urinary antimony concentrations were 0.42 ng/mg creatinine, and 95% of the infants had antimony concentrations <2.6 ng/mg creatinine.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In discussing exposure to antimony, it is important to consider what form of antimony a person is exposed to and its availability. High concentrations of antimony may be found in the contaminated soil and sediment. In water, the pentavalent state is predominant, although significant levels of trivalent antimony and methylated antimony compounds exist. People who live or work near sources of antimony such as smelters, coal-fired power plants, and refuse incinerators may be exposed to high levels of antimony in airborne dust, soil, and vegetation. People who live near or work at waste sites that receive slag from smelters or fly ash from power plants and refuse incinerators may also be exposed to higher than background levels. Exposure routes would include either inhalation of contaminated air or ingestion of contaminated soil or vegetation. Similarly, people who are exposed to soot and smoke in fires, such as firefighters, may be exposed to high levels of antimony. Occupational exposure to antimony appears to be highest for those involved in the production and processing of antimony and antimony oxide. Workers in battery-forming areas of lead-storage battery plants may be exposed to high levels of stibine.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of antimony is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of antimony.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. For inorganic salts, the solubility product coupled with stability constants for the ionic species in solution are the factors determining how much of the compound goes

into solution; the solubility in terms of the number of milligrams of the parent compound in solution, as used for organic compounds, is not meaningful. All of the solubility products and stability constants for antimony and its compounds, required for determining the antimony species in natural water and their concentrations, are not available. Other physical and chemical properties in Table 4-2 for which there are no data are generally not well defined for antimony and its compounds or are not useful in determining their environmental fate.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2014, became available in March of 2016. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Information on the production, import, and use of antimony and antimony trioxide is readily available (Carapella 1978; Grund et al. 2012; Llewellyn 1989; Plunkert 1982; USGS 2004, 2015). However, information on the production, import, and use patterns of other antimony compounds is not available, and is needed to assess human exposure to these compounds. Except for the recycling of batteries, little information is available concerning the disposal of antimony and its compounds. More detailed information regarding the form of antimony that is disposed of and the disposal methods is necessary to assess the potential exposure to these compounds.

Environmental Fate. In assessing human exposure, the form (valence state, compound, adsorption, coprecipitation, particle size) of antimony and its availability must be considered. This information is site specific and is not always available in the literature.

Bioavailability from Environmental Media. Antimony is poorly absorbed following inhalation and oral exposure (Felicetti et al. 1979a, 1979b; Gerber et al. 1982; Thomas et al. 1973). Dermal exposure to high levels of antimony trioxide resulted in death in rabbits (Myers et al. 1978). The application area was occluded, suggesting that at least some forms of antimony can be absorbed through the skin. Although there is no information on the absorption efficiency of antimony from environmental media in humans, there is evidence in animals that it is absorbed. The vegetation and soils at sites near antimony smelters are heavily contaminated with antimony. Elevated levels of antimony in various tissues were observed in animals living near the smelter (Ainsworth et al. 1990). An animal study designed to measure the rate of

absorption of antimony from environmental media would be useful in assessing the toxicological significance of levels of antimony in the air and soil near hazardous waste sites.

Food Chain Bioaccumulation. Studies indicate that phytoremediation is possible with accumulation and uptake of antimony in plants (Anawar et al. 2011; Baceva et al. 2014; Pan et al. 2010; Tschan et al. 2008, 2009). Studies on fish and aquatic organisms indicate that the bioconcentration of antimony is low; however, the studies are older (Callahan et al. 1979; EPA 1980; Maher 1986). Newer studies on the bioconcentration of antimony in fish and biomagnification in higher trophic levels of animals are needed.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of antimony in contaminated media at hazardous waste sites are needed so that the information obtained on levels of antimony in the environment can be used in combination with the known body burden of antimony to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Levels of antimony in the water, soil, and sediment are dependent on the site. Levels of antimony in the air in Japan were found to be highest from brake abrasion dust (Iijima et al. 2009). Concentrations of antimony in water were higher near ore and mining sites. Levels of antimony in the soil and sediment were dependent on the distance from the source of contamination; higher levels were found for soil depths of 0–5 cm (near the surface) and in sediment found upstream (near the site) (Filella et al. 2009b; Migon and Mori 1999).

Exposure Levels in Humans. Antimony has been detected in urine, blood, hair, and nails in individuals exposed to background levels of antimony (CDC 2015; Miekeley et al. 1998; Takagi et al. 1986, 1988). Antimony is one of the chemicals measured in urine samples collected from NHANES participants; the most recent data are from the 2011–2012 survey. More recent data are needed to assess occupational exposure of humans to antimony. A NOES was conducted; however, the data were from 1981–1983 (NIOSH 1989).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Antimony levels were measured in urinary samples from NHANES participants ≥6 years old; however, biomonitoring data are not available for younger children.

Monitoring studies are needed for infants and young children particularly since there is the potential for exposure from clothing and household items treated with antimony containing flame retardants.

Child health data needs relating to susceptibility are discussed in Section 3.13.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The information amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance; however, no exposure registries for antimony were located. Antimony is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. Antimony will be considered in the future when chemical selection is made for sub-registries to be established.

6.8.2 Ongoing Studies

No ongoing environmental fate studies for antimony or antimony compounds were identified using the NIH RePORTER (2015) database.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring antimony, its metabolites, and other biomarkers of exposure and effect to antimony. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Methods for the analytical determination of antimony in biological materials are similar to those used for environmental samples. Methodological differences are a function of the level of antimony in the sample, digestion procedures required to solubilize the sample, and level of potentially interfering substances in the type of sample. Antimony occurs at very low levels in biological samples. The accurate determination of trace levels of antimony in these samples may require special methods (e.g., neutron activation) that are both sensitive and selective.

Atomic absorption spectroscopy (AAS) and inductively coupled plasma-atomic emission spectroscopy (ICP-AES), with or without preconcentration or separation steps, are the most commonly employed methods. Atomic absorption has three variant methods involving direct aspiration into a flame, atomization in an electrically heated carbon rod, or generation of stibine that is then passed into a heated silica tube.

Instrumental neutron activation analysis (INAA), with or without chemical separation, has very good sensitivity and selectivity for antimony, and it has the advantage of being able to measure many elements simultaneously. However, it is slow, costly, and requires special facilities. INAA is favored for surveys where trace levels of many elements are to be determined. It is often required for measuring antimony in tissues in which the antimony level is very low. The neutron activation analysis of antimony requires an exposure to neutron fluxes for 6 hours to 2 days. After the exposure period, the samples are kept for several days before counting. This allows the activity of short half-lived isotopes to decline, and thus

improves accuracy of the analysis (Iyengar et al. 1978). Nondestructive INAA can be used to measure concentrations to levels somewhat below 1 ppm. Nondestructive methods are not only advantageous because of reduced sample handling, but also because they are independent of the sample matrix and of the efficiency of the digestion or extraction procedure. While this is generally adequate for antimony determinations in hair and lung tissues, the antimony levels in blood serum and kidney tissues are usually too low to measure without preconcentration (Iyengar et al. 1978). Detection limits may be limited by interferences from matrix elements such as sodium, potassium, phosphorus, and bromine. Lower detection limits (approximately 0.006 ppm) can be obtained by digestion and solvent extraction to eliminate interferences (Mok and Wai 1988).

Determining which form of antimony (usually Sb(III) and Sb(V)) is present in a sample is difficult; however, methods have been developed to do so in both biological and environmental samples. Speciation is possible with the use of anion exchange liquid chromatography (post-column photo-oxidation) and hydride generation atomic fluorescence spectrometry (high-performance liquid chromatography-ultraviolet-hydride generation-atomic fluorescence spectrometry [HPLC-(UV) -HG-AFS]) as the detection system (De Gregori et al. 2007; Quiroz et al. 2011).

Sector field-high resolution-inductively coupled plasma-mass spectrometry (SF-HR-ICP-MS) was used to determine the antimony concentration in gunshot residues on hands. SF-HR-ICP-MS is a selective method with high sensitivity. The SF-HR-ICP-MS method is useful for detecting antimony at very low concentrations in samples (Sarkis et al. 2007). Analytical methods and detection limits for antimony in biological materials are provided in Table 7-1. Antimony contained in biological materials such as hair and nails can be determined by using the same analytical techniques as for blood and tissue, but suitable procedures for dissolving the sample matrix must be used (Takagi et al. 1986, 1988).

7.2 ENVIRONMENTAL SAMPLES

Analytical methods for measuring antimony in environmental samples generally determine the total antimony content of the sample. Separate procedures for determining specific antimony compounds have been developed. Acid digestion to assure release of antimony from the sample matrix is a crucial step in the analysis of environmental samples. Unless the particular type of sample has been well studied, it is usually important to experiment with different digestion procedures. For the release of antimony from

Table 7-1. Analytical Methods for Determining Antimony in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood, tissue, or hair[a]	Acid digestion	Method 8005, ICP-AES[b]	No data	106% at 10 µg antimony	NIOSH 1985
Gunshot residue on hand	Extraction and dilution	SF-HR-ICP-MS[b]	No data	No data	Sarkis et al. 2007
Pine needles (tissue)	Digestion	ICP-AES[b]	0.41 µg/L	85%	Anderson and Isaacs 1995
Marine biota (algae and mollusks)	Extraction, centrifugation, evaporation	HPLC-(UV)-HG-AFS[c]	0.007 µg /L	96–107%	De Gregori et al. 2007
Urine, serum, blood, liver, and lung tissue	Acid digestion	ICP-MS[b]	0.0.1 µg//L (urine serum, blood); 0.7 ng/g (liver); 0.8 ng/g (lung)	No data	Delves et al. 1997
Urine	Microwave digestion	HPLC-HG-AFS[c]	0.01 µg/L	No data	Quiroz et al. 2011
Feces	Digest with concentration HCl/HNO_3; extract hexane/hydrogen peroxide; nickel matrix modifier	Graphite furnace AAS[b]	No data	96.9%, mean	Bio/Dynamic 1990

[a]Method extended to hair (Takagi et al. 1986).
[b]Measures total antimony.
[c]Measures antimony species.

AAS = atomic absorption spectrometry; AES = atomic emission spectroscopy AFS = atomic fluorescence spectrometry; HCl = hydrochloric acid; HG = hydride generation; HNO_3 = nitric acid; HPLC = High-performance liquid chromatography; HR = high resolution; ICP = inductively coupled plasma; MS = mass spectrometry; SF = sector field; UV = ultraviolet

soil, hydrogen fluoride mixed with perchloric acid or another strong acid is generally required. In the determination of trace metals, major concerns include contamination and loss. Contamination can be introduced from impurities in reagents, containers, or laboratory dust. Losses may also occur due to adsorption of the analyte onto container walls. In the case of antimony, a common source of loss is volatilization during acid digestion or ashing in an AAS furnace. Losses are prevented by application of a procedure that utilizes acid digestion in a closed-vessel microwave digestion system. Microwave digestion prevents the escape, and thus the loss, of the volatile antimony compounds. Insoluble antimony silicate is dissociated with the aid of the hydrogen fluoride (Amereih et al. 2005).

The most common methods used for analysis of antimony in environmental samples are AAS with either flame or graphite furnace and ICP-AES. Calorimetric methods were used for the determination of antimony before the widespread use of AAS. The best known calorimetric method is the rhodamine B method in which a pink complex is formed when pentavalent antimony reacts with rhodamine B in the presence of an excess of chloride ions (APHA 1972). The complex is extracted into an organic solvent and the absorbance measured at 565 nm. Trivalent antimony must be oxidized to the pentavalent state with nitric, sulfuric, and perchloric acids. Water and waste water samples can be analyzed for antimony by EPA Test Methods 220.1 (atomic absorption, direct aspiration), 220.2 (atomic absorption, furnace technique), and 200.7 (inductively coupled plasma-atomic emission spectroscopy) (EPA 1983b). These methods are suitable for groundwater, surface water, and domestic and industrial effluents.

In open ocean water and in other water samples with a low antimony concentration, pre-concentration and/or separation procedure involving co-precipitation, chelation, selective adsorption, or hydride formation is required before analysis (Andresen and Salbu 1982; Apte and Howard 1986; Maher 1986; Sturgeon et al. 1985). The atomic absorption wavelength used for antimony is 217.6 nm. In the presence of lead concentrations of the order of 1 g/L, however, a spectral interference may occur at this resonance line, and the line at 231.1 nm should be used instead. The spectral absorption of antimony is reduced when the concentration of acid increases using direct aspiration. Therefore, it is important to match the concentration of acid in standards and samples (EPA 1983b). Laser-induced fluorescence in graphite furnace (LIF-GIF) with intensified charge coupled device (ICCD) detection is also utilized for environmental samples (water and sediment). Due to its high sensitivity, this method can detect antimony at very low concentrations in the sample (Enger et al. 1995).

Similarly, liquid chromatography-HG-AFS is utilized for antimony speciation in environmental samples (tap water, river water, etc.). The method has low detection limits and is effective in determining which

species of antimony is present. Detection limits were 0.9, 0.5, and 0.7 µg/L for Sb(III), Sb(V), and $TMSbCl_2$, respectively (Vinas et al. 2006). Flow injection-HG-AAS was also utilized in the speciation of antimony in environmental water samples. This method has a low detection limit and is low in cost (Zheng et al. 2006).

Analytical methods and detection limits for antimony in environmental media are provided in Table 7-2.

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of antimony is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of antimony.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. Methods for determining antimony in biological materials are well developed, and there are methods available to most laboratories that are satisfactory for testing biological samples that naturally contain high concentrations of antimony for occupational exposure testing (Delves et al. 1997; NIOSH 1985; Quiroz et al. 2011). Antimony can occur at very low levels in many biological materials; thus, methods such as INAA that require special facilities must often be used to achieve adequate sensitivity (Iyengar et al. 1978). Standardized methods are available from NIOSH and other sources to measure antimony in blood, urine, and tissue (Delves et al. 1997; NIOSH 1985; Quiroz et al. 2011). Several

Table 7-2. Analytical Methods for Determining Antimony in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Filter collection and acid digestion	Method 301, colorimetric (Rhodamine B)	1.0 µg	95–102% between 2 and 10 µg antimony	APHA 1972
	Filter collection and acid digestion and reduction of Sb(V) with NaI	Hydride generation-AAS	0.004 µg	10% accuracy at 40 ng antimony	De Doncker et al. 1983
Air (stibine)	Filter collection (20-L sample) on $HgCl_2$-coated silica gel; desorption and treatment with concentrated HCl, ceric sulfate, and liquid extraction	NIOSH 6008, colorimetric (Rhodamine B)	No data	98.6% between 0.12 and 1.0 µg antimony	NIOSH 1987
Water, waste water	Acid digestion	Method 204.1, AAS/direct aspiration	200 µg /L	96 and 97% at 5 and 15 mg antimony/L, respectively	EPA 1983a
	Acid digestion, sample solutions should contain 2% HNO_3	Method 204.2, AAS/furnace technique	3 µg/L	Not applicable	EPA 1983a
	Filter and acidify sample	Method 200.7, ICP-AES	32 µg/L	Not applicable	EPA 1983a
Water	Extraction, shaken with chloroform	AAS	0.00001 µg	80%	de la Calle-Guntinas et al. 1991
Water	Digestion	ICP-AES	0.41 µg/L	106–111%	Anderson and Isaacs 1995
Drinking water/riverine water/ estuarine water	Dilution, acidification with nitric acid	LIF-GF-ICCD	$5x10^{-9}$–$2x10^{-8}$ µg	No data	Enger et al. 1995
Tap water/river water	Centrifuged and filtered	LC-HG-AFS	Sb(V): 0.5 µg/L; Sb(III): 0.9 µg/L; $TMSbCl_2$: 7 µg/L	Sb(V): 96–99%; Sb(III): 97–99%; $TMSbCl_2$: 96–100%	Vinas et al. 2006
River water	Absorption onto TiO_2	HG-AAS	Sb(V): 0.06 ng/mL; Sb(III): 0.05 µg/L	Sb(V): 98–104.5%; Sb(III): 95.5–98%	Zheng et al. 2006

Table 7-2. Analytical Methods for Determining Antimony in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Dried, microwave digestion	HPLC-ID-ICP-MS	No data	No data	Amereih et al. 2005
Marine sediment	Dilution, acidification with nitric acid	IF-GF-ICCD	$3x10^{-8}$ µg	No data	Enger et al. 1995
Soil, sediment, sludge, solid waste	Digestion with 4:1 HNO_3 and HCl[a]	Method 3050 (modified)[a] ICP-AES	No data	3% accuracy at 33 ppm antimony	EPA 1986
Soil and sediment	Suspension	GFAAS	0.03 µg/g	No data	Lopez-Garcia et al. 1997
Food	Acid digestion and resin separation following irradiation	INAA	0.1–0.3 ppb	No data	Cunningham 1987

[a]The digestion procedure in Method 3050 is not suitable for antimony. A satisfactory digestion procedure has been proposed by Kimbrough and Wakakuwa (1989).

AAS = atomic absorption spectrometry; AES = atomic emission spectroscopy; GF = graphite furnace; GFAAS = graphite furnace atomic absorption spectrometry; HCl = hydrochloric acid; HG = hydride generation; $HgCl_2$ = mercuric chloride; HNO_3 = nitric acid; HPLC = high-performance liquid chromatography; ICCD = intensified charge coupled device; ICP = inductively coupled plasma; ID = isotopic dilution; INAA = instrumental neutron activation analysis; LC = liquid chromatography; LIF = laser-induced fluorescence; MS = mass spectrometry; NaI = sodium iodide; NIOSH = National Institute for Occupational Safety and Health; Sb(V) = antimony (+5)

authors have reported that antimony concentrations in hair, nails, blood, or urine are elevated in exposed individuals (Katayama and Ishidi 1987); blood and urine levels are considered suitable biomarkers of exposure for antimony. Available analytical methods are capable of determining the levels of antimony in these media in both background and occupationally exposed persons.

Effect. No biomarkers of effect were identified for antimony.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Methods for determining antimony in environmental media are well developed and adequate. Standardized methods are available from EPA, NIOSH, and other sources (Amereih et al. 2005; APHA 1972; Cunningham 1987; De Doncker et al. 1983; de la Calle-Guntinas et al. 1991; Enger et al. 1995; EPA 1983a, 1986; NIOSH 1987; Vinas et al. 2006; Zheng et al. 2006). Since most analytical methods measure total antimony, the methods for analyzing for the parent compound and degradation product are identical.

7.3.2 Ongoing Studies

No ongoing studies for examining analytical methods to detect antimony or antimony compounds were identified using the NIH RePORTER (2015) database.

8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates that are intended to serve as screening levels. They are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

An acute-duration inhalation MRL of 0.001 mg Sb/m^3 was derived for antimony. The MRL is based on a $BMCL_{HEC}$ of 0.035 mg Sb/m^3 calculated from the incidence data for squamous metaplasia of the epiglottis in mice (NTP 2016) and an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability).

A chronic-duration inhalation MRL of 0.0003 mg Sb/m^3 was derived for antimony. The MRL is based on a $BMCL_{HEC}$ of 0.008 mg Sb/m^3 calculated from the incidence data for chronic lung inflammation in female rats (Newton et al. 1994) and an uncertainty factor of 30 (3 for extrapolation from animals to humans using dosimetric adjustments and 10 for human variability).

An acute-duration oral MRL of 1 mg Sb/kg/day was derived based on a NOAEL of 99 mg Sb/kg/day for focal ulceration of the forestomach in mice (NTP 1992) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

An intermediate-duration oral MRL of 0.0006 mg Sb/kg/day was derived based on a NOAEL of 0.064 mg Sb/kg/day for decreased serum glucose levels in rats (Poon et al. 1998) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

The international and national regulations, advisories, and guidelines regarding antimony in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Antimony

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2015
	Antimony trisulfide	Group 3[a]	
	Antimony trioxide	Group 2B[b]	
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines (antimony and compounds)		WHO 2011
	Guideline value	0.02 mg/L (20 µg/L)[c]	
	TDI	6 µg/kg body weight[d]	
NATIONAL			
Regulations and guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)		ACGIH 2015
	Antimony and compounds	0.5 mg/m^3	
	Antimony trioxide	L[e]	
	Stibine	0.1 ppm	
AIHA	ERPGs (stibine)		AIHA 2015
	ERPG-1	Insufficient data	
	ERPG-2	0.5 ppm	
	ERPG-3	1.5 ppm	
DOE	PACs		DOE 2012a
	PAC-1[f]		
	Antimony	0.5 mg/m^3	
	Antimony pentasulfide	2.5 mg/m^3	
	Antimony potassium tartrate	1.7 mg/m^3	
	Antimony trichloride	0.94 mg/m^3	
	Antimony trioxide	0.6 mg/m^3	
	Stibine	0.14 ppm	
	PAC-2[f]		
	Antimony	0.5 mg/m^3	
	Antimony pentasulfide	22 mg/m^3	
	Antimony potassium tartrate	1.7 mg/m^3	
	Antimony trichloride	0.94 mg/m^3	
	Antimony trioxide	0.6 mg/m^3	
	Stibine	1.5 ppm	
	PAC-3[f]		
	Antimony	80 mg/m^3	
	Antimony pentasulfide	130 mg/m^3	
	Antimony potassium tartrate	220 mg/m^3	
	Antimony trichloride	150 mg/m^3	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Antimony

Agency	Description	Information	Reference
NATIONAL (*cont.*)			
DOE (*cont.*)	PACs		
	PAC-3[f] (*cont.*)		
	Antimony trioxide	96 mg/m^3	
	Stibine	9.6 ppm	
NAS	AEGLs (stibine)[g]		AEGLs 2008
	AEGL 1		
	10-minute	NR[h]	
	30-minute	NR[h]	
	60-minute	NR[h]	
	4-hour	NR[h]	
	8-hour	NR[h]	
	AEGL 2		
	10-minute	4.2 ppm	
	30-minute	2.9 ppm	
	60-minute	1.5 ppm	
	4-hour	0.36 ppm	
	8-hour	0.18 ppm	
	AEGL 3		
	10-minute	28 ppm	
	30-minute	19 ppm	
	60-minute	9.6 ppm	
	4-hour	2.4 ppm	
	8-hour	1.2 ppm	
	Hazardous air pollutant (antimony compounds)	Yes	EPA 2013a 42 USC 7412
NIOSH	REL (up to 10-hour TWA)		NIOSH 2015a, 2015b
	Antimony and compounds	0.5 mg/m^3	
	Stibine	0.1 ppm (0.5 mg/m^3)	
	IDLH		
	Antimony and compounds	50 mg/m^3	
	Stibine	5 ppm	
OSHA	PEL (8-hour TWA) for general industry (antimony and compounds)	0.5 mg/m^3	OSHA 2013 29 CFR 1910.1000, Table Z-1
	PEL (8-hour TWA) for shipyards (antimony and compounds)	0.5 mg/m^3	OSHA 2014 29 CFR 1915.1000 Table Z

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Antimony

Agency	Description	Information	Reference
NATIONAL (*cont.*)			
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act		EPA 2013b 40 CFR 116.4
	Antimony potassium tartrate, Antimony trichloride, antimony trioxide	Yes	
	Drinking water standards and health advisories (antimony)		EPA 2012
	1-day health advisory for a 10-kg child	0.01 mg/L	
	10-day health advisory for a 10-kg child	0.01 mg/L	
	DWEL	0.01 mg/L	
	Life-time health advisory	0.006 mg/L	
	National primary drinking water standards		EPA 2009
	MCL (antimony)	0.006 mg/L	
	National recommended water quality criteria: human health for the consumption of		EPA 2015b
	Water plus organism	5.6 µg/L	
	Organism only	640 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2013c 40 CFR 117.3
	Antimony potassium tartrate	100 pounds	
	Antimony trichloride, antimony trioxide	1,000 pounds	
c. Food			
FDA	EAFUS	No data[i]	FDA 2013
	Allowable level for antimony in bottled water	0.006 mg/L	FDA 2014 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2015
	Antimony and compounds	No data	
	Antimony trioxide	A2[j]	
	Stibine	No data	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Antimony

Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	Carcinogenicity classification	No data	IRIS 1987, 1995
	RfC		
	Antimony trioxide	2 x 10^{-4} mg/m^3	
	RfD		
	Antimony	4 x 10^{-4} mg/kg/day	
	Superfund, emergency planning, and community right-to-know		
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2013d 40 CFR 372.65
	TSCA chemical lists and reporting periods	No data	EPA 2014 40 CFR 712.30
DHHS	Carcinogenicity classification	No data	NTP 2014

[a]Group 3: not classifiable as to carcinogenicity to humans.
[b]Group 2B: possibly carcinogenic to humans.
[c]Concentrations in groundwater <0.001 µg/L; concentrations in surface water <0.2 µg/L; and concentrations in drinking water appear to be <5 µg/L.
[d]Based on a NOAEL of 6.0 mg/kg body weight per day for decreased body weight gain and reduced food and water intake in a 90-day study in which rats were administered potassium antimony tartrate in drinking water, using an uncertainty factor of 1,000 (100 for interspecies and intraspecies variation and 10 for the short duration of the study).
[e]Endnote L: Exposure by all routes should be carefully controlled to levels as low as possible.
[f]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2012b).
[g]Interim values.
[h]NR = not recommended due to insufficient data.
[i]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
[j]A2: Suspected human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DHHS = Department of Health and Human Services; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; EAFUS = Everything Added to Food in the United States; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NOAEL = no-observed-adverse-effect level;NRC = National Research Council; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TDI = tolerable daily intake; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; WHO = World Health Organization

This page is intentionally blank.

9. REFERENCES

Abbasi SA. 1989. Sub-microdetermination of antimony(III) and antimony(V) in natural and polluted waters and total antimony in biological materials by flameless AAS following extractive separation with N-p-methoxyphenyl-2-furylacrylohydroxamic acid. Anal Lett 22:237-256.

Abdel-Mequid M, Habib YA, Abdallah A, et al. 1967. The effect of antibilharzial antimonial compounds on the percentage of oxygen saturation of blood. J Egypt Med Assoc 50:369-374.

ACGIH. 1989. Threshold limit values and biological exposure indices for 1989-1990. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*ACGIH. 2015. Antimony, antimony hydride, and antimony trioxide. In: TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

*Acquire. 1989. Acquire database. September 7, 1989.

*Adlercreutz H. 1995. Phytoestrogens: Epidemiology and a possible role in cancer protection. Environ Health Perspect 103(Supp 7):103-112.

*AEGLs. 2008. Acute exposure guideline levels (AEGLs) for stibine (antimony hydride) 7803-52-3. [Interim]. U.S. Environmental Protection Agency. http://www2.epa.gov/sites/production/files/2014-09/documents/stibine_interim_ornl_jun_2008c.pdf. November 9, 2015.

*AIHA. 2015. Current ERPG Values (2015). Fairfax, VA: American Industrial Hygiene Association. https://www.aiha.org/get-involved/AIHAGuidelineFoundation/EmergencyResponsePlanningGuidelines/Documents/2015%20ERPG%20Levels.pdf. November 9, 2015.

*Ainsworth N, Cooke JA, Johnson MS. 1990. Distribution of antimony in contaminated grassland: 2. Small mammals and invertebrates. Environ Poll 65:79-87.

*Ainsworth N, Cooke JA, Johnson MS. 1991. Behavior and toxicity of antimony in the short-tailed field vole (*Microtus agrestis*). Ecotoxicol Environ Saf 21(2):165-170.

*Alkhawajah A, Larbi EB, Jain S, et al. 1992. Subacute toxicity of pentavalent antimony compounds in rats. Hum Exp Toxicol 11(4):283-288.

*Alkhawajah AM, Jain S, Larbi EB. 1996. Effects of antimony compounds on foetal development in rats. J Appl Anim Res 10:15-24.

*Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies of Experimental Biology, 1987-2008, 2041.

---

* Cited in text
+ Cited in supplemental document

9. REFERENCES

*Alvarez M, Malecot CO, Gannier F, et al. 2005. Antimony-induced cardiomyopathy in guinea-pig and protection by L-carnitine. Br J Pharmacol 144(1):17-27. 10.1038/sj.bjp.0706030.

*Amereih S, Meisel T, Scholger R, et al. 2005. Antimony speciation in soil samples along two Austrian motorways by HPLC-ID-ICP-MS. J Environ Monit 7(12):1200-1206. 10.1039/b510321e.

*Anawar HM, Freitas MC, Canha N, et al. 2011. Arsenic, antimony, and other trace element contamination in a mine tailings affected area and uptake by tolerant plant species. Environ Geochem Health 33(4):353-362. 10.1007/s10653-011-9378-2.

*Andersen EM, Cruz-Saldarriaga M, Llanos-Cuentas A, et al. 2005. Comparison of meglumine antimoniate and pentamidine for Peruvian cutaneous leishmaniasis. Am J Trop Med Hyg 72(2):133-137.

*Andersen ME, Clewell HJ, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87(2):185-205.

*Andersen ME, Krishnan K. 1994. Relating *in vitro* to *in vivo* exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, and replacement. New York, NY: Marcel Dekker, Inc., 9-25.

*Anderson KA, Isaacs B. 1995. Simultaneous determination of arsenic, selenium, and antimony in environmental samples by hydride generation for inductively coupled plasma atomic emission spectrometry. J AOAC Int 78(4):1055-1060.

Andreae MO. 1983. The determination of the chemical species of some of the "hydride elements" (arsenic, antimony, tin and germanium) in seawater: Methodology and results. NATO Conference 49:1-19.

*Andreae MO, Froelich PN. 1984. Arsenic, antimony, germanium biogeochemistry in the Baltic Sea. Tellus Ser B 36B:101-117.

*Andreae MO, Byrd JT, Froehlich PN. 1983. Arsenic, antimony, germanium, and tin in the Tejo estuary, Portugal: Modeling a polluted estuary. Environ Sci Technol 17:731-737.

*Andresen B, Salbu B. 1982; Determination of trace elements in seawater using magnesium hydroxide scavenger as preconcentration agent. Radiochem Radioanal Lett 52:19-27.

+*Angrisani M, Lampa E, Lisa M, et al. 1988. Vasomotor reactivity and postnatal exposure to antimony trichloride. Curr Ther Res 43:153-159.

Anonymous. 1977. Arsenic, selenium and antimony in urine and air analytical method by hydride generation and atomic absorption spectroscopy. Health Lab Sci 14:53-58.

*APHA. 1972. Methods of air sampling and analysis. Washington, DC: American Public Health Association, 285-289.

*Apte SC, Howard AG. 1986. Determination of dissolved inorganic antimony(V) and antimony(II1) species in natural waters by hydride generation atomic absorption spectrometry. J Anal Atom Spectrom 1:221-225.

*Arimoto R, Duce RA. 1987. Air-sea transfer of trace elements. Adv Chem Ser 216:131-150.

*Asakura K, Satoh H, Chiba M, et al. 2009. Genotoxicity studies of heavy metals: Lead, bismuth, indium, silver and antimony. J Occup Health 51(6):498-512.

*Asta MP, Nordstrom KD, McCleskey BR. 2012. Simultaneous oxidation of arsenic and antimony at low and circumneutral pH, with and without microbial catalysis. Appl Geochem 27(1):281-291. 10.1016/j.apgeochem.2011.09.002.

*ATSDR. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; Notice. Agency for Toxic Substances and Disease Registry. Fed Regist 54(174):37618-37634.

*ATSDR. 1992. Toxicological profile for antimony and compounds. Atlanta, GA: Agency for Toxic Substances and Disease Registry, U.S. Public Health Service.

*ATSDR. 2015. Antimony. Full SPL data. Substance priority list (SPL) resource page. Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/SPL/resources/index.html. July 6, 2016.

Auguston JH. 1976. Soldiers' water vessels as a lead source. Ann Occup Hyg 19:169-171.

Aulenbach DB, Meyer MA, Beckwith E, et al. 1987. Removal of heavy metals in POTW. Environ Prog 6:91-98.

*Austin LS, Millward GE. 1988. Simulated effects of tropospheric emissions on the global antimony cycle. Atmos Environ 22:1395-1403.

*Avento JM, Touval I. 1980. Flame retardants (antimony). In: Kirk-Othmer encyclopedia of chemical technology. Vol. 10, 3rd ed. New York, NY: John Wiley and Sons, Inc., 355-356.

Ayhan M, Krajewski W, Krueger J. 1982. Possibility of the formation of arsine and stibine during the simultaneous melting of lead-antimony and lead-calcium battery scrap. Erzmetall 35:155-158.

*Baceva K, Stafilov T, Matevski V. 2014. Bioaccumulation of heavy metals by endemic *Viola* species from the soil in the vicinity of the As-Sb-Tl mine "allchar' Republic of Macedonia. Int J Phytoremediation 16(4):347-365. 10.1080/15226514.2013.783551.

*Bailey MR, Ansoborlo E, Guilmette RA, et al. 2007. Updating the ICRP human respiratory tract model. Radiat Prot Dosimetry 127(1-4):31-34.

*Bailly R, Lauwerys R, Buchet JP, et al. 1991. Experimental and human studies on antimony metabolism: Their relevance for the biological monitoring of workers exposed to inorganic antimony. Br J Ind Med 48(2):93-97.

*Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8(4):471-486.

*Basinger MA, Jones MM. 1981. Structural requirements for chelate antidotal efficacy in acute antimony(II1) intoxication. Res Commun Chem Pathol Pharmacol 32:355-363.

Bauer CF, Andren AW. 1988. Variability of particulate trace element emissions from the Columbia coal-fired power plant, Portage, Wisconsin. Sci Total Environ 68:251-266.

Beijer K, Jernelov A. 1986. Sources, transport and transformation of metals in the environment. In: Friberg L, Norberg JF, Urik VB, eds. Handbook on the toxicology of metals. 2nd ed. New York, NY: Elsevier, 68-83.

+*Belyaeva AP. 1967. [The effect of antimony on reproduction.] Gig Truda Prof Zabol 11:32. (Russian)

*Belzile N, Chen Y, Filella M. 2011. Human exposure to antimony: I. Sources and intake. Crit Rev Environ Sci 41:1309-1373.

*Bentley R, Chasteen TG. 2002. Microbial methylation of metalloids: Arsenic, antimony, and bismuth. Microbiol Mol Biol Rev 66(2):250-271.

*Berger GS, ed. 1994. Epidemiology of endometriosis. In: Endometriosis: Modern surgical management of endometriosis. New York, NY: Springer-Verlag, 3-7.

Berman JD, Gallalee JF, Gallalee JV. 1988. Pharmacokinetics of pentavalent antimony (Pentostam) in hamsters. Am J Trop Med Hyg 39:41-45.

*Bio/Dynamics. 1985. A three month inhalation toxicity study of antimony trioxide in the rat followed by a recovery period. Prepared by Bio/dynamics, Inc., E. Millstone, NJ for the Antimony Oxide Industry Association, Washington, DC. 83-7646.

*Bio/Dynamics. 1990. A one year inhalation toxicity study of antimony trioxide in the rat (with a one year recovery period). Prepared by Bio/dynamics, Inc., E. Millstone, NJ for the Antimony Oxide Industry Association, Washington, DC.

*Bodek I, Lyman WJ, Reehl RF, et al. 1988. Environmental inorganic chemistry properties processes and estimation methods. New York, NY: Pergamon Press, 7.1-1 to 7.1-5.

*Boex TJ, Padgham C, Nurse PA, et al. 1998. Antimony and sudden infant death syndrome. Lancet 351(9109):1102-1103.

*Bradley WR, Frederick WG 1941. The toxicity of antimony-animal studies. Ind Med 10:15-22.

Brannon JM, Patrick WH. 1985. Fixation and mobilization of antimony in sediments. Environ Pollut Ser B 9:107-126.

Braun H, Maul S, Vogg H. 1983. [Heavy metals in the gas phase - selected examples for emission and environmental impact measurements.] Kornforschungszentrum Karlsruhe GmbH, Laboratorium fur Isotpoentechnik, Karlsruhe, Germany. (German)

+*Brieger H, Semisch CW III, Stasney J, et al. 1954. Industrial antimony poisoning. Ind Med Surg 23:521-523.

*Bromberger-Barnea B, Stephens NL. 1965. Effects of antimony on myocardial performance in isolated and intact canine hearts. Am Ind Hyg Assoc J 26:404-408.

Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. St. Louis, MO: The C.V. Mosby Company, 40, 103-104, 109-110, 123124, 127-128, 165-166.

Buddenmeier RW, Hunt JR. 1988. Transport of colloidal contaminants in groundwater: Radionuclide migration at the Nevada Test Site. Appl Geochem 1:535-548.

Burroughs GE, Horan J. 1981. Health hazard evaluation report no. HHE-80023-804. Becton-Dickinson Company, Columbus, Nebraska. Cincinnati, OH: Hazard Evaluations and Technical Assistance Branch, Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health. PB82191222.

*Callahan MA, Slimak MW, Gabel NW, et al. 1979. Water-related environmental fate of 129 priority pollutants. Vol. 1. Washington, DC: Office of Water Planning and Standards, U.S. Environmental Protection Agency. EPA440479029a, 5-l to 5-8.

*Carapella SC. 1978. Antimony and antimony alloys. In: Kirk-Othmer encyclopedia of chemical technology. Vol. 3, 3rd ed. New York, NY: John Wiley and Sons, Inc., 96-105.

Cassady ME, Etchison B. 1976. Walk-through survey of Chemetron Corporation Inorganic Chemicals Division. Cincinnati, OH: Industrial Hygiene Section, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health.

Casto BC, Meyers J, DiPaolo JA. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res 39:193-198.

*Cavallo D, Iavicoli I, Setini A, et al. 2002. Genotoxic risk and oxidative DNA damage in workers exposed to antimony trioxide. Environ Mol Mutagen 40(3):184-189. 10.1002/em.10102.

*CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf. May 2, 2016.

*CDC. 2015. Fourth national report on human exposure to environmental chemicals, updated tables (February 2015). Centers for Disease Control and Prevention. http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf. December 14, 2015.

*Charles River Laboratories. 2006. Clinical laboratory parameters for Crl:CD(SD) rats. March, 2006. http://www.criver.com/files/pdfs/rms/cd/rm_rm_r_clinical_parameters_cd_rat_06.aspx. September 13, 2016.

*Chen YW, Deng TL, Filella M, et al. 2003. Distribution and early diagenesis of antimony species in sediments and porewaters of freshwater lakes. Environ Sci Technol 37(6):1163-1168.

*Chulay JD, Fleckenstein L, Smith DH. 1988. Pharmacokinetics of antimony during treatment of visceral leishmaniasis with sodium stibogluconate or meglumine antimoniate. Trans Royal Soc Tropical Med 82:69-72.

*Clewell HJ, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

CLPSD. 1989. Contract Laboratory Program Statistical Database. Viar and Company, Alexandria, VA.

*Coelho DR, De-Carvalho RR, Rocha RC, et al. 2014a. Effects of *in utero* and lactational exposure to SbV on rat neurobehavioral development and fertility. Reprod Toxicol 50:98-107. 10.1016/j.reprotox.2014.10.016.

*Coelho DR, Miranda ES, Saint'Pierre TD, et al. 2014b. Tissue distribution of residual antimony in rats treated with multiple doses of meglumine antimoniate. Mem Inst Oswaldo Cruz 109(4):420-427.

+*Colak EH, Yomralioglu T, Nisanci R, et al. 2015. Geostatistical analysis of the relationship between heavy metals in drinking water and cancer incidence in residential areas in the Black Sea region of Turkey. J Environ Health 77(6):86-93.

*Cole H, Frederick RE, Healy RP, et al. 1984. Preliminary findings of the priority pollutant monitoring project of the nationwide urban runoff program. J Water Pollut 56:898-908.

+*Cooper DA, Pendergrass EP, Vorwald AJ, et al. 1968. Pneumoconiosis among workers in an antimony industry. Am J Roentgenol Rad Ther Nuclear Med 103:495-508.

*Costa LG, Aschner M, Vitalone A, et al. 2004. Developmental neuropathology of environmental agents. Annu Rev Pharmacol Toxicol 44:87-110. 10.1146/annurev.pharmtox.44.101802.121424.

Costantini S, Giordano R, Rizzica M, et al. 1985. Applicability of anodic-stripping voltammetry and graphite furnace atomic-absorption spectrometry to the determination of antimony in biological matrixes: A comparative study. Analyst 110:1355-1359.

*Cotten M, Logan ME. 1966. Effects of antimony on the cardiovascular system and intestinal smooth muscle. J Pharmacol Exp Ther 151:7-22.

*Cotton FA, Wilkinson G. 1966. Advanced inorganic chemistry. A comprehensive text. New York, NY: Interscience Publishers, 498-503.

Craig AB Jr., Vandervort R, Burton DJ, et al. 1981. Environmental and occupational protection in the secondary lead industry. DHHS (NIOSH) Pub1 ISS 81-114, 360-398.

Crecelius EA, Bothner MH, Carpenter R. 1975. Geochemistries of arsenic, antimony, mercury, and related elements in sediments of Puget Sound. Environ Sci Technol 9:325-333.

Crecelius EA, Johnson CJ, Hofer GC. 1974. Contamination of soils near a copper smelter by arsenic, antimony and lead. Water Soil Pollut 3:337-342.

*Cruz A, Rainey PM, Herwaldt BL, et al. 2007. Pharmacokinetics of antimony in children treated for leishmaniasis with meglumine antimoniate. J Infect Dis 195(4):602-608. 10.1086/510860.

*Cullen A, Kiberd B, Matthews T, et al. 1998. Antimony in blood and urine of infants. J Clin Pathol 51(3):238-240.

*Cunningham WC. 1987. Radiochemical determination of arsenic, chromium, molybdenum, antimony and selenium in foods. J Radioanal Nucl Chem 113:423-430.

*Cutter GA. 1992. Kinetic controls on metalloid speciation in seawater. Mar Chem 40(1–2):65-80. 10.1016/0304-4203(92)90048-F.

9. REFERENCES

Cyr F, Mehra MC, Mallet VN. 1987. Leaching of a chemical contaminants from a municipal landfill site. Bull Environ Contam Toxicol 38:775-782.

*Dams R, Vandecasteele C, Desmet B, et al. 1988. Element concentrations in the air of an indoor shooting range. Sci Total Environ 77:1-14.

*Dancaster CP, Duckworth WC, Matthews REP. 1966. Stokes-Adams attacks following sodium antimonylgluconate (Triostam). S Afr Med J 40:1029-1030.

Dean JA. 1985. Langes handbook of chemistry. 13th ed. New York, NY: McGraw-Hill, 4-21 to 2-23.

*De Doncker K, Dumarey R, Dams R, et al. 1983. Determination of antimony in atmospheric particulate matter by hydride generation and atomic absorption spectrometry. Anal Chim Acta 153:33-40.

*De Gregori I, Quiroz W, Pinochet H, et al. 2007. Speciation analysis of antimony in marine biota by HPLC-(UV)-HG-AFS: Extraction procedures and stability of antimony species. Talanta 73(3):458-465. 10.1016/j.talanta.2007.04.015.

*De La Calle-Guntinas MB, Madrid Y, Camara C. 1991. Determination of antimony(III) and antimony(V) in water by selective extraction with lactic acid-Malachite Green followed by graphite furnace atomic absorption spectrometry. Anal Chim Acta 247(1):7-12.

DeLaune RD, Smith CJ. 1985. Release of nutrients and metals following oxidation of freshwater and saline sediment. J Environ Qua1 14:164-168.

*Delves HT, Sieniawska CE, Fell GS, et al. 1997. Determination of antimony in urine, blood and serum and in liver and lung tissues of infants by inductively coupled plasma mass spectrometry. Analyst 122(11):1323-1329.

Demanze C, Rugroff L, Karleskind A. 1984. [Determination of metals in cosmetic and body hygiene products.] Parfums Cosmet Aromes 58:69-70, 73-74, 76, 78. (French).

+*Dernehl CU, Nau CA, Sweets HH. 1945. Animal studies on the toxicity of inhaled antimony trioxide. J Ind Hyg Toxicol 27:256-262.

*Dezateux C, Delves HT, Stocks J, et al. 1997. Urinary antimony levels in infants are low and unrelated to age or passive smoking. Child Care Health Dev 23(5):423-424.

+*Dieter MP, Jameson CW, Elwell MR, et al. 1991. Comparative toxicity and tissue distribution of antimony potassium tartrate in rats and mice dosed by drinking water or intraperitoneal injection. J Toxicol Environ Health 34(1):51-82. 10.1080/15287399109531548.

*DOE. 2009a. Analysis of background distributions of metals in the soil at Lawrence Berkeley National Laboratory. U.S. Department of Energy. LBNL-1782E. http://www2.lbl.gov/ehs/erp/assets/pdfs/Background%20Metals%20in%20Soil%20Report0409.pdf. March 18, 2016.

*DOE. 2009b. A review of metal concentrations measured in surface soil samples collected on and around the Hanford Site. U.S. Department of Energy. PNNL-18577. http://www.pnl.gov/main/publications/external/technical_reports/PNNL-18577.pdf. March 15, 2016.

*DOE. 2012a. Table 3: PACs by CASRN (pdf). PAC Rev 27 Tables - PAC data and chemical properties presented in pdf and excel tables. Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 27 for Chemicals of Concern - March 2012. Oak Ridge, TN: U.S. Department of Energy. http://energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-27-chemicals-concern-march-2012. March 4, 2015.

*DOE. 2012b. Protective action criteria (PAC): Chemicals with AEGLs, ERPGs, & TEELs. Definition of PACs (AEGLs, ERPGs or TEELs). Protective Action Criteria (PAC) with AEGLs, ERPGs, & TEELs: Rev. 27 for Chemicals of Concern - March 2012. Oak Ridge, TN: U.S. Department of Energy. http://energy.gov/ehss/protective-action-criteria-pac-aegls-erpgs-teels-rev-27-chemicals-concern-march-2012. March 24, 2015.

Donaldson H. 1976. Industrial hygiene survey of Texas Smelting and Refining Division of National Lead Industries, Laredo, Texas. Cincinnati, OH: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

Donaldson H, Gentry S. 1975. II. Air sampling industrial hygiene survey: The Harshaw Chemical Company, Gloucester City, New Jersey. Cincinnati, OH: Department of Health, Education and Welfare, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health.

*Dorea JG, Merchan-Hamann E, Ryan DE, et al. 1989. Retention of antimony in hair during leishmaniasis treatment. Clin Chim Acta 179:341-345.

Drummond GS, Kappas A. 1981. Potent heme-degrading action of antimony and antimony-containing parasiticidal agents. J Exp Med 153:245-256.

*Dunn JT. 1928. A curious case of antimony poisoning. Analyst 531:532-533.

*Dutkiewicz VA, Parekh PP, Husain L. 1987. An evaluation of regional elemental signatures relevant to the northeastern United States. Atmos Environ 21:1033-1044.

*Eagle H, Germuth G, Magnuson HJ, et al. 1947. The protective action of BAL in experimental antimony poisoning. J Pharmacol Exp Ther 89(2):196-204.

*Eckel WP, Langley WD. 1988. A background-based ranking technique for assessment of elemental enrichment in soils at hazardous waste sites. In: Proceedings of the 9th Superfund '88 National Conference, Washington, DC, November 28-30, 1988, 282-285.

Eckel WP, Jacob TA. 1988. Ambient levels of 24 dissolved metals in U.S. surface and grounds waters. Presented before the Division of Environmental Chemistry, American Chemical Society, Los Angeles, CA, September 25-30, 1988. Preprint of extended abstract. Alexandria, VA: Viar and Company, 371-372.

*Eckel WP, Jacob TA. 1989. Ambient concentrations of 25 "dissolved" and "total" metals in U.S. surface waters. Alexandria, VA: Viar and Company.

*Edel J, Marafante E, Sabbioni E, et al. 1983. Metabolic behaviour of inorganic forms of antimony in the rat. Proc Heavy Metal Environ Int Conf 1:574-577.

9. REFERENCES

*Ek CJ, Dziegielewska KM, Habgood MD, et al. 2012. Barriers in the developing brain and neurotoxicology. Neurotoxicology 33(3):586-604. 10.1016/j.neuro.2011.12.009.

*Elinder CG, Friberg L. 1986. Antimony. In: Handbook on the toxicology of metals. Vol. II. 2nd ed. Amsterdam: Elsevier Science Publishers, 26-42.

*Elliott BM, Mackay JM, Clay P, et al. 1998. An assessment of the genetic toxicology of antimony trioxide. Mutat Res 415(1-2):109-117.

*Enger J, Marunkov A, Chekalin N, et al. 1995. Direct detection of antimony in environmental and biological samples at trace concentrations by laser-induced fluorescence in graphite furnace with an intensified charge coupled device. J Anal Atom Spectrom 10(8):539-549.

*EPA. 1980. Ambient water quality criteria for antimony. Washington, DC: Office of Water Regulations and Standards Criteria Division, U.S. Environmental Protection Agency. EPA440580020. PB81117319.

EPA. 1981. Treatability manual. Volume I. U.S. Environmental Protection Agency. EPA600282001a 1.4.7-l to 1.4.7-5.

*EPA. 1983a. Antimony metal, antimony trioxide, and antimony sulfide response to the Interagency Testing Committee. Fed Regist 48:717-725.

*EPA. 1983b. Methods for chemical analysis of water and wastes. Cincinnati, OH: Environmental Monitoring and Support Laboratory, U.S. Environmental Protection Agency. EPA600479020, 204.1-l to 204.1-2; 204.2-l to 204.2-2; Metals-20 to Metals-29.

EPA. 1985. 40 CFR Parts 117 and 302: List of hazardous substances and reportable quantities. Fed Regist 50(65):13476. 119

*EPA. 1986. 40 CFR Parts 117 and 302: List of hazardous substances and reportable quantities. Fed Regist 51(188):34541.

EPA. 1987. U40 CFR Parts 117 and 302: List of hazardous substances and reportable quantities. Fed Regist 52(50):8168.

*EPA. 1988. Analysis of clean water act effluent guidelines pollutants. Summary of the chemicals regulated by industrial point source category. 40 CFR Parts 400-475.

*EPA. 1990. Interim methods for development of inhalation reference concentrations. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment, Office of Research and Development. EPA600890066A. PB90238890.

*EPA. 1997. Special report on environmental endocrine disruption: An effects assessment and analysis. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA630R96012.

*EPA. 2000. National air pollutant emission trends, 1900-1998. U.S. Environmental Protection Agency. EPA454R00002. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=2000ETJA.txt. March 17, 2016.

*EPA. 2005. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency, Office of Environmental Information. EPA260B05001.

*EPA. 2009. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency, Office of Ground Water and Drinking Water. EPA816F090004. http://water.epa.gov/drink/contaminants/upload/mcl-2.pdf. March 4, 2015.

*EPA. 2012. 2012 Edition of the drinking water standards and health advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Water. EPA822S12001. http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf. March 4, 2015.

*EPA. 2013a. Title 42 - The public health and welfare. Chapter 85 - Air pollution prevention and control. Subchapter I - programs and activities. Part A - Air quality and emission limitations. Hazardous air pollutants. United States Code. U.S. Environmental Protection Agency. 42 USC 7412. http://www.gpo.gov/fdsys/pkg/USCODE-2013-title42/pdf/USCODE-2013-title42-chap85-subchapI-partA-sec7412.pdf. April 9, 2015.

*EPA. 2013b. Subchapter D-water programs. Designation of hazardous substances. Code of Federal Regulations. U.S. Environmental Protection Agency. 40 CFR 116.4. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol22/pdf/CFR-2014-title40-vol22-sec116-4.pdf. March 4, 2015.

*EPA. 2013c. Subpart A - General provisions. Determination of reportable quantities. Code of Federal Regulations. U.S. Environmental Protection Agency. 40 CFR 117.3. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol22/pdf/CFR-2014-title40-vol22-sec117-3.pdf. March 4, 2015.

*EPA. 2013d. Subpart D - Specific toxic chemical listings. Chemicals and chemical categories to which this part applies. Code of Federal Regulations. U.S. Environmental Protection Agency. 40 CFR 372.65. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol28/pdf/CFR-2014-title40-vol28-sec372-65.pdf. March 4, 2015.

*EPA. 2014. Subpart B - Manufacturers reporting - preliminary assessment information. Chemical lists and reporting periods. Code of Federal Regulations. U.S. Environmental Protection Agency. 40 CFR 712.30. http://www.gpo.gov/fdsys/pkg/CFR-2014-title40-vol31/pdf/CFR-2014-title40-vol31-sec712-30.pdf. April 9, 2015.

*EPA. 2015a. Air quality system (AQS). Data files. Annual summary data. U.S. Environmental Protection Agency. http://aqsdr1.epa.gov/aqsweb/aqstmp/airdata/download_files.html. December 2, 2015.

*EPA. 2015b. National recommended water quality criteria. Washington, DC: U.S. Environmental Protection Agency, Office of Water, Office of Science and Technology. http://water.epa.gov/scitech/swguidance/standards/criteria/current/index.cfm. July 23, 2015.

*EPA. 2016. Air emissions inventories. 2011 National Emissions Inventory (NEI) data. U.S. Environmental Protection Agency. https://www.epa.gov/air-emissions-inventories/2011-national-emissions-inventory-nei-data. March 21, 2016.

*FDA. 2013. Everything added to food in the United States (EAFUS). Washington, DC: U.S. Food and Drug Administration. http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting. January 8, 2014.

*FDA. 2014. Subchapter B - Requirements for specific standardized beverages. Bottled water. Code of Federal Regulations. Food and Drug Administration. 21 CFR 165.110. http://www.gpo.gov/fdsys/pkg/CFR-2014-title21-vol2/pdf/CFR-2014-title21-vol2-sec165-110.pdf. March 4, 2015.

*Felicetti SW, Thomas RG, McClellan RO. 1974a. Retention of inhaled antimony-124 in the beagle dog as a function of temperature of aerosol formation. Health Phys 26:525-531.

*Felicetti SW, Thomas RG, McClellan RO. 1974b. Metabolism of two valence states of inhaled antimony in hamsters. Am Ind Hyg Assoc J 355:292-300.

Fergusson JE, Forbes EA, Schroeder RJ, et al. 1986. The elemental composition and sources of house dust and street dust. Sci Total Environ 50:217-221.

*Filella M, Belzile N, Chen YW. 2002. Antimony in the environment: a review focused on natural waters: II. Relevant solution chemistry. Earth-Science Reviews 59(1-4):265-285. 10.1016/S0012-8252(02)00089-2.

*Filella M, Philippo S, Belzile N, et al. 2009b. Natural attenuation processes applying to antimony: A study in the abandoned antimony mine in Goesdorf, Luxembourg. Sci Total Environ 407(24):6205-6216. 10.1016/j.scitotenv.2009.08.027.

*Filella M, Williams PA, Belzile N. 2009a. Antimony in the environment: Knowns and unknowns. Huanjing Huaxue 6(2):95-105. 10.1071/EN09007.

+*Fleming AJ. 1982. The toxicity of antimony trioxide. Sponsored by E.I. Du Pont de Nemours and Co., Wilmington, DE. OTS215027.

*Fomon SJ. 1966. Body composition of the infant: Part 1: The male reference infant. In: Faulkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

*Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35(Suppl 5):1169-1175.

Foster RB. 1989. Antimony mobility in soil using soil TLC. Prepared by Springborn Life Sciences, Inc., Wareham, MA for the Antimony Oxide Industry Association, Washington, DC.

*Freedman LD, Doak GO, Long GG. 1978. Antimony compounds. In: Kirk-Othmer encyclopedia of chemical technology. Vol. 3, 3rd ed. New York, NY: John Wiley and Sons, Inc., 105-128.

*Friedrich K, Vieira FA, Porrozzi R, et al. 2012. Disposition of antimony in rhesus monkeys infected with *Leishmania braziliensis* and treated with meglumine antimoniate. J Toxicol Environ Health A 75(2):63-75. 10.1080/15287394.2012.624826.

*Garbos S, Bulska E, Hulanicki A, et al. 2000. Determination of total antimony and antimony(V) by inductively coupled plasma mass spectrometry after selective separation of antimony(III) by solvent extraction with N-benzoyl-N-phenylhydroxylamine. Spectrochimica Acta Part B: Atomic Spectroscopy 55(7):795-802. 10.1016/S0584-8547(00)00212-3.

*Gebel T, Birkenkamp P, Luthin S, et al. 1998a. Arsenic(III), but not antimony(III), induces DNA-protein crosslinks. Anticancer Res 18(6A):4253-4257.

*Gebel T, Claussen K, Dunkelberg H. 1998b. Human biomonitoring of antimony. Int Arch Occup Environ Health 71(3):221-224.

*Gellhorn A, van Dyke HB. 1946. The correlation between distribution of antimony in tissues and chemotherapeutic effect in experimental leishmaniasis. J Pharmacol Exp Ther 88:162-172.

*Gellhorn A, Tupikova NA, van Dyke HB. 1946. The tissue distribution and excretion of four organic antimonials after single or repeated administration to normal hamsters. J Pharmacol Exp Ther 87:169-180.

*Gerber GB, Maes J, Eykens B. 1982. Transfer of antimony and arsenic to the developing organism. Arch Toxicol 49:159-168.

*Gerhardsson L, Brune D, Nordberg GF, et al. 1982. Antimony in lung, liver and kidney tissue from deceased smelter workers. Scand J Work Environ Health 8:201-208.

Gerritse RG, Vriesema R, Dalenberg JW, et al. 1982. Effect of sewage sludge on trace element mobility in soils. J Environ Qua1 11:359-364.

Ghaleb HA, Shoeb HA, el-Gawhary N, et al. 1979. Acute toxicity studies of some new organic trivalent antimonials. J Egypt Med Assoc 62:45-62.

Gillain G, Brihaye C. 1985. A routine speciation method for a pollution survey of coastal seawater. Oceanol Acta 8:231-235.

*Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect 101(Supp 2):65-71.

Gladney ES, Gordon GE. 1978. Coal combustion: Source of toxic elements in urban air. J Environ Sci Health A13:481-491.

*Gladney ES, Perrin DR, Robinson RD, et al. 1984. Multitechnique determination of elemental concentrations in NBS Urban Air Particulate SRM 1648 and evaluation of its use for quality assurance. J Radioanal Nucl Chem 83:379-386.

*Goodwin LG, Page JE. 1943. A study of the excretion of organic antimonials using a polarographic procedure. Biochem J 37:198-209.

Gordon GE, Sheffield AE. 1986. Variability of compositions of particles released by coal-fired power plants. ACS Symp Ser 248-254.

Greenburg RR, Zoller WH, Gordon GE. 1978. Composition and size distribution of particles released in refuse incinerators. Environ Sci Technol 12:566-573.

9. REFERENCES

+*Gross P, Brown JHU, Hatch TF. 1952. Experimental endogenous lipoid pneumonia. Am J Pathol 28:211-221.

+*Gross P, Brown JHU, Westrick ML, et al. 1955. Toxicological study of calcium halophosphate phosphors and antimony trioxide. I. Acute and chronic toxicity and some pharmacologic aspects. Arch Ind Health 11:473-478.

+*Groth DH, Stettler LE, Burg JR, et al. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. J Toxicol Environ Health 18:607-626.

*Grund SC, Hanusch K, Breunig HJ, et al. 2012. Antimony and antimony compounds. In: Ullman's encyclopedia of industrial chemistry. Wiley-VCH Verlag GmbH & Co. 10.1002/14356007.a03_055.pub2.

Gudzovskij GA. 1983. Antimony, alloys and compounds. In: Encyclopedia of Occupational Health and Safety, 176-178.

*Gurnani N, Sharma A, Talukder G. 1992b. Cytotoxic effects of antimony trichloride on mice *in vivo*. Cytobios 70(281):131-136.

*Gurnani N, Sharma A, Talukder G. 1992a. Comparison of the clastogenic effects of antimony trioxide on mice *in vivo* following acute and chronic exposure. Biometals 5(1):47-50.

*Gurnani N, Sharma A, Talukder G. 1993. Comparison of clastogenic effects of antimony and bismuth as trioxides on mice *in vivo*. Biol Trace Elem Res 37(2-3):281-292. 10.1007/bf02783802.

*Guzelian PS, Henry CJ, Olin SS. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences and Press Institute Press.

*Haldar AK, Sen P, Roy S. 2011. Use of antimony in the treatment of leishmaniasis: Current status and future directions. Mol Biol Int 2011:571242. 10.4061/2011/571242.

*Hansen C, Tsirigotaki A, Bak SA, et al. 2010. Elevated antimony concentrations in commercial juices. J Environ Monit 12(4):822-824. 10.1039/b926551a.

Hansen ID, Fisher HL. 1980. Elemental distribution in coal fly ash particles. Environ Sci Technol 14:1111-1117.

*Hantson P, Leonard ED, Crutzen-Fayt MC, et al. 1996. Cytogenetic observations after meglumine antimoniate therapy for visceral leishmaniasis. Pharmacotherapy 16(5):869-871.

*Han-Wen S, Xiao-Quan S, Zhe-Ming N. 1982. Selective separation and differential determination of antimony(III) and antimony(V) by solvent extraction with N-benzoyl-N-phenylhydroxylamine and graphite-furnace atomic-absorption spectrometry using a matrix-modification technique. Talanta 29(7):589-593.

*Harris JW. 1956. Studies on the mechanism of drug-induced hemolytic anemia. J Lab Clin Med 47:760-775.

Hasanen E, Pohjola V, Hahkala M. 1986. Emissions from power plants fueled by peat, coal, natural gas and oil. Sci Total Environ 54:29-51.

Hay DJ, Finkelstein A, Klicius R. 1986. The national incinerator testing and evaluation program two-stage incinerator combustion tests. Chemosphere 15:1201-1212.

*HazDat. 2007. Antimony and compounds. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

Henderson A, Jolliffe D. 1985. Cardiac effects of sodium stibogluconate. Br J Clin Pharmacol 19:73-77.

*Herbst KA, Rose G, Hanusch K, et al. 1985. Antimony and antimony compounds. In: Ullmann's encyclopedia of industrial chemistry. Vol. A3, 5th ed. Free Republic of Germany: VCH Vereage gesellschaft Weinheim, 55-76.

*Herrera CE, Kirmeyer HJ, Hoyt BP. 1982. Seattle distribution system corrosion control study: Volume III: Potential for drinking water contamination from tin/antimony solder. U.S. Environmental Protection Agency, Washington, DC. EPA600282013. PB82231242.

Hewitt PJ. 1988. Accumulation of metals in the tissues of occupationally exposed workers. Environ Geochem Health 10:113-116.

*Hext PM, Pinto PJ, Rimmel BA. 1999. Subchronic feeding study of antimony trioxide in rats. J Appl Toxicol 19(3):205-209.

*Hillamo R, Pacyna JM, Bartonova A. 1988. Characterization of aerosols during long-range transport episodes of air pollution to Norway. J Aerosol Sci 19:1257-1261.

+*Hiraoka N. 1986. The toxicity and organ-distribution of antimony after chronic administration to rats. J Kyoto Prefect Univ Med 95:997-1017.

*Hoel DG, Davis DL, Miller AB, et al. 1992. Trends in cancer mortality in 15 industrialized countries, 1969-1986. J Natl Cancer Inst 84(5):313-320.

*Honey M. 1960. The effects of sodium antimony tartrate on the myocardium. Br Heart J 22:601-616.

*Hopper JF, Barrie LA. 1988. Regional and background aerosol trace elemental composition observed in eastern Canada. Tellus Ser B 40B:446-462.

+*Horton JR, Gawroski CL, Newton PE, et al. 1986. Evaluation of the acute toxicity, irritation, sensitization, and subchronic dermal toxicity of antimony thioantimonate lubricant. ADA166 873/O.

+*Houpt K, Zgoda JC, Stahlbaum CC. 1984. Use of taste repellants and emetics to prevent accidental poisoning of dogs. Am J Vet Res 45:1501-1503.

*HSDB. 2005a. Antimony, elemental. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 22, 2015.

*HSDB. 2005b. Antimony trichloride. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 22, 2015.

9. REFERENCES

*HSDB. 2009a. Antimony sulfide. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 22, 2015.

*HSDB. 2009b. Stibine. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 22, 2015.

*HSDB. 2013. Antimony trioxide. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 22, 2015.

*HSDB. 2014. Antimony potassium tartrate. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 22, 2015.

*Huang H, Shu SC, Shih JH, et al. 1998. Antimony trichloride induces DNA damage and apoptosis in mammalian cells. Toxicology 129(2-3):113-123.

*IARC. 2015. Agents classified by the IARC monographs. Volumes 1–114. Lyon, France: International Agency for Research on Cancer. http://monographs.iarc.fr/ENG/Classification/List_of_Classifications_Vol1-114.pdf. November 9, 2015.

*Iavicoli I, Caroli S, Alimonti A, et al. 2002. Biomonitoring of a worker population exposed to low antimony trioxide levels. J Trace Elem Med Biol 16(1):33-39. 10.1016/s0946-672x(02)80006-2.

*ICRP. 1981. Metabolic data for antimony. Limits for intakes of radionuclides by workers (ICRP Publication 30, Part 3). International Commission on Radiological Protection. Ann ICRP 6(2/3):46-49.

*ICRP. 1994. Molybdenum. In: Age-dependent doses to members of the public from intake of radionuclides: Part 2. Ingestion dose coefficients. ICRP publication 67. Tarrytown, NY: International Commission on Radiological Protection. Elsevier Science, Inc., 45-47.

*Iijima A, Sato K, Fujitani Y, et al. 2009. Clarification of the predominant emission sources of antimony in airborne particulate matter and estimation of their effects on the atmosphere in Japan. Huanjing Huaxue 6(2):122-132. 10.1071/EN08107.

*IRIS. 1987. Antimony; CASRN 7440-36-0. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0006_summary.pdf. November 9, 2015.

*IRIS. 1995. Antimony trioxide; CASRN 1309-64-4. Integrated Risk Information System. Washington, DC: U.S. Environmental Protection Agency. http://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0676_summary.pdf. November 9, 2015.

Ives JA, Doughty PA, Casuccio GS. 1984. Superfund and fugitive dust - an air quality study. Proc Air Pollut Contr Assoc 6:84-100.

*Iyengar GV, Kasperek K, Feinendegen LE. 1978. Determination of certain selected bulk and trace elements in bovine liver matrix using neutron activation analysis. Phys Med Biol 23:66-77.

Iyengar GV, Kasperek K, Feinendegen LE. 1982. Determination of cobalt, copper, iron, mercury, manganese, antimony, selenium, and zinc in milk samples. Sci Total Environ 24:267-274.

Iyengar GV, Tanner JT, Wolf WR, et al. 1987. Preparation of a mixed human diet material for the determination of nutrient elements, selected toxic elements and organic nutrients: A preliminary report. Sci Total Environ 61:235-252.

*Jablonska-Czapla M, Szopa S, Grygoyc K, et al. 2014. Development and validation of HPLC-ICP-MS method for the determination inorganic Cr, As and Sb speciation forms and its application for Plawniowice Reservoir (Poland) water and bottom sediments variability study. Talanta 120:475-483. 10.1016/j.talanta.2013.11.092.

*Jenkins RO, Craig PJ, Goessler W, et al. 1998. Antimony leaching from cot mattresses and sudden infant death syndrome (SIDS). Hum Exp Toxicol 17(3):138-139.

*Johnson CA, Moench H, Wersin P, et al. 2005. Solubility of antimony and other elements in samples taken from shooting ranges. J Environ Qual 34(1):248-254.

*Johnson DL, Davis BL, Dzubay TG, et al. 1984. Chemical and physical analyses of Houston aerosol for interlaboratory comparison of source apportionment procedures. Atmos Environ 18:1539-1553.

Joliffe DS. 1985. Nephrotoxicity of pentavalent antimonials. Lancet 1:584.

+*Jones RD. 1994. Survey of antimony workers: Mortality 1961-1992. Occup Environ Med 51(11):772-776.

Jones W, Gamble J. 1984. Epidemiological-environmental study of lead acid battery workers. I. Environmental study of five lead acid battery plants. Environ Res 35:1-10.

*Kanematsu N, Hara M, Kada T. 1980. Ret assay and mutagenicity studies on metal compounds. Mutat Res 77:109-116.

+*Kanisawa M, Schroeder HA. 1969. Life term studies on the effects of trace elements on spontaneous tumors in mice and rats. Cancer Res 29:892-895.

*Katayama Y, Ishida N. 1987. Determination of antimony in nail and hair by thermal neutron activation analysis. Radioisotopes 36:103-107.

*Kearns GL, Abdel-Rahman SM, Alander SW, et al. 2003. Developmental pharmacology-drug disposition, action, and therapy in infants and children. N Engl J Med 349(12):1157-1167. 10.1056/NEJMra035092.

Kempton S, Sterritt RM, Lester JN. 1983. Factors affecting the fate and behavior of toxic elements in the activated sludge process. Environ Pollut Ser A 32~51-78.

*Kentner M, Leinemann M, Schaller KH, et al. 1995. External and internal antimony exposure in starter battery production. Int Arch Occup Environ Health 67(2):119-123.

+*Kim HA, Heo Y, Oh SY, et al. 1999. Altered serum cytokine and immunoglobulin levels in the workers exposed to antimony. Hum Exp Toxicol 18(10):607-613.

Kim KW, Choi BS, Kang SK, et al. 1997. Assessment of workers' exposure to antimony trioxide in Korea. J Occup Health 39(4):345-348.

*Kimbrough DE, Wakakuwa JR. 1989. Acid digestion for sediments, sludges, soils, and soil wastes. A proposed alternative to EPA SW 846 Method 3050. Environ Sci Technol 23:898-900.

*King LD. 1988. Retention of metals by several soils of the southeastern United States. J Environ Qua1 17:239-246.

*Kirkland D, Whitwell J, Deyo J, et al. 2007. Failure of antimony trioxide to induce micronuclei or chromosomal aberrations in rat bone-marrow after sub-chronic oral dosing. Mutat Res 627(2):119-128. 10.1016/j.mrgentox.2006.10.012.

*Kobayashi A, Ogra Y. 2009. Metabolism of tellurium, antimony and germanium simultaneously administered to rats. J Toxicol Sci 34(3):295-303.

*Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29(18):4430-4433.

*Kowalczyk GS, Gordon GE, Rheingrover SW. 1982. Identification of atmospheric particulate sources in Washington, D.C. Using chemical element balances. Environ Sci Technol 16:79-90.

*Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

*Krishnan K, Anderson ME, Clewell HJ, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures. Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

*Kubo T, Urano K, Utsumi H. 2002. Mutagenicity characteristics of 255 environmental chemicals. J Health Sci 48(6):545-554.

*Kuroda K, Endo G, Okamoto A, et al. 1991. Genotoxicity of beryllium, gallium and antimony in short-term assays. Mutat Res 264(4):163-170.

*Kuryshev YA, Wang L, Wible BA, et al. 2006. Antimony-based antileishmanial compounds prolong the cardiac action potential by an increase in cardiac calcium currents. Mol Pharmacol 69(4):1216-1225. 10.1124/mol.105.019281.

*Landsberger S, Jervis RE, Kajrys G, et al. 1983. Characterization of trace elemental pollutants in urban snow using proton induced x-ray emission and instrumental neutron activation analysis. Int J Environ Anal Chem 16:95-130.

*Lantzsch H, Gebel T. 1997. Genotoxicity of selected metal compounds in the SOS chromotest. Mutat Res 389(2-3):191-197.

Lantzy RJ, Mackenzie FT. 1979. Atmospheric trace metals: Global cycles and assessment of man's impact. Geochem Cosmochem Acta 43:511-525.

*Lawn SD, Armstrong M, Chilton D, et al. 2006. Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. Trans R Soc Trop Med Hyg 100:264-269.

*Lauwers LF, Roelants A, Rosseel PM, et al. 1990. Oral antimony intoxications in man. Crit Care Med 18(3):324-326.

Lee RE Jr., Crist HL, Riley AE, et al. 1975. Concentration and size of trace metal emissions from a power plant, a steel plant and a cotton gin. Environ Sci Technol 9:643-647.

*Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

*Lehr CR, Kashyap DR, McDermott TR. 2007. New insights into microbial oxidation of antimony and arsenic. Appl Environ Microbiol 73(7):2386-2389. 10.1128/aem.02789-06.

*Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballantyne B, Marrs T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

*Lewis RJ. 2012. Antimony pentoxide. AQF750. In: Sax's dangerous properties of industrial medicine. Hoboken, NJ: John Wiley & Sons, Inc., 341-342.

*Li T. 2011. Antimony and antimony alloys. In: Kirk-Othmer encyclopedia of chemical toxicology. John Wiley & Sons, Inc. 10.1002/0471238961.011420091209.a01.pub3.

*Liao YH, Yu HS, Ho CK, et al. 2004. Biological monitoring of exposures to aluminium, gallium, indium, arsenic, and antimony in optoelectronic industry workers. J Occup Environ Med 46:931-936.

*Lima MI, Arruda VO, Alves EV, et al. 2010. Genotoxic effects of the antileishmanial drug Glucantime. Arch Toxicol 84(3):227-232. 10.1007/s00204-009-0485-0.

*Lippincott SW, Ellerbrook LD, Rhees M, et al. 1947. A study of the distribution and fate of antimony when used as tartar emetic and fuadin in the treatment of American soldiers with *Schistosomiasis japonica*. J Clin Invest 26:370-378.

*Livingston AL. 1978. Forage plant estrogens. J Toxicol Environ Health 4(2-3):301-324.

Llewellyn TO. 1989. Antimony. In: Minerals yearbook metals and minerals 1987, Volume 1. Pittsburgh, PA: Bureau of Mines, U.S. Department of the Interior. http://digicoll.library.wisc.edu/cgi-bin/EcoNatRes/EcoNatRes-idx?id=EcoNatRes.MinYB1987v1. March 16, 2016.

*Longerich HP, Friel JK, Fraser C, et al. 1991. Analysis of the drinking water of mothers of neural tube defect infants and of normal infants for 14 selected trace elements by inductively coupled plasma-mass spectrometry (ICP-MS). Can J Appl Spectrosc 36(1):15-21.

*Lopez-Garcia I, Sanchez-Merlos M, Hernandez-Cordoba M. 1997. Arsenic and antimony determination in soils and sediments by graphite furnace atomic absorption spectrometry with slurry sampling. Spectrochimica Acta Part B Atomic Spectroscopy 52(4):437-443.

*Ludersdorf R, Fuchs A, Mayer P, et al. 1987. Biological assessment of exposure to antimony and lead in the glass-producing industry. Int Arch Occup Environ Health 59:469-474.

*Luo J, Bai Y, Liang J, et al. 2014. Metagenomic approach reveals variation of microbes with arsenic and antimony metabolism genes from highly contaminated soil. PLoS ONE 9(10):e108185. 10.1371/journal.pone.0108185.

*Maciaszczyk-Dziubinska E, Wawrzycka D, Wysocki R. 2012. Arsenic and antimony transporters in eukaryotes. Int J Mol Sci 13(3):3527-3548. 10.3390/ijms13033527.

*Maher W. 1986. Measurement of total antimony in marine organisms and waters by stibine generation and atomic absorption spectrometry. Anal Lett 19:295-305.

*Mansour MM, Rasoul AAA, Schulert AR. 1967. Anti-bilharzial antimony drugs. Nature 214:819-820.

*Mansour SE, Reese HH. 1965. Experimental antimony toxicity on lower motor neurons and muscles of mice. Exp Parasitol 16:148-157.

Markham MC, Hannan MC, Liu L, et al. 1958. Photochemical properties of antimony trioxide. J Phys Chem 62:989-992.

+*Marmo E, Matera MG, Acampora R, et al. 1987. Prenatal and postnatal metal exposure: Effect on vasomotor reactivity development of pups. Curr Ther Res 42:823-838.

Martinson JP. 1988. Biotransformation of antimony oxide in natural sediments under aerobic and anaerobic conditions. Prepared by Springborn Life Sciences, Inc., Wareham, MA for the Antimony Oxide Industry Association, Washington, DC.

Maxfield D, Rodriguez JM, Buettner M, et al. 1974. Heavy metal pollution in the sediments of the Coeur d'Alene River delta. Environ Pollut 7:1-6.

*Mayr U, Butsch A, Schneider S. 1992. Validation of two *in vitro* test systems for estrogenic activities with zearalenone, phytoestrogens and cereal extracts. Toxicology 74(2-3):135-149.

+*Mendy A, Gasana J, Vieira ER. 2012. Urinary heavy metals and associated medical conditions in the US adult population. Int J Environ Health Res 22(2):105-118.

Metzger M, Braun H. 1989. Striping voltammetric determination of traces of antimony(II1) and antimony(V) in natural waters after selective extraction. Anal Chim Acta 189:263-275.

*Miekeley N, Carneiro MTW, Silveira CLP. 1998. How reliable are human hair reference intervals for trace elements? Sci Total Environ 218(1):9-17.

*Migliore L, Cocchi L, Nesti C, et al. 1999. Micronuclei assay and FISH analysis in human lymphocytes treated with six metal salts. Environ Mol Mutagen 34(4):279-284.

*Migon C, Mori C. 1999. Arsenic and antimony release from sediments in a Mediterranean estuary. Hydrobiologia 392(1):81-88.

*Michalke K, Wickenheiser EB, Mehring M, et al. 2000. Production of volatile derivatives of metal(loid)s by microflora involved in anaerobic digestion of sewage sludge. Appl Environ Microbiol 66(7):2791-2796.

*Milford JB, Davidson CL. 1985. The sizes of particulate trace elements in the atmosphere-a review. Air Pollut Contr Assoc 35:1249-1257.

Miller MH. 1973. Antimony. U.S. Geological Survey Professional Paper 820. Alexandria VA: U.S. Geological Survey, 45-50.

Minear RA, Ball RO, Church RL. 1981. Database for influent heavy metals in publicly owned treatment works. Cincinnati, OH: Municipal Environmental Research laboratory, U.S. Environmental Protection Agency. EPA 600/52-81-220, 1-5.

*Miranda ES, Miekeley N, De-Carvalho RR, et al. 2006. Developmental toxicity of meglumine antimoniate and transplacental transfer of antimony in the rat. Reprod Toxicol 21(3):292-300. 10.1016/j.reprotox.2005.09.010.

*Miravet R, López-Sánchez JF, Rubio R. 2006. Leachability and analytical speciation of antimony in coal fly ash. Anal Chim Acta 576(2):200-206. 10.1016/j.aca.2006.06.003.

*Mitsunobu S, Harada T, Takahashi Y. 2006. Comparison of antimony behavior with that of arsenic under various soil redox conditions. Environ Sci Technol 40(23):7270-7276. 10.1021/es060694x.

Mok WM, Wai CM. 1987. Simultaneous extraction of trivalent and pentavalent antimony and arsenic species in natural waters for neutron activation analysis. Anal Chem 59:233-236.

*Mok WM, Wai CM. 1988. Determination of arsenic and antimony in biological materials by solvent extraction and neutron activation. Talanta 35:183-186.

*Mok WM, Wai CM. 1990. Distribution and mobilization of arsenic and antimony species in the Coeur d'Alene River, Idaho. Environ Sci Technol 24:102-108.

Molokhia A, Lilley JD. 1986. Unusual levels of trace elements in dental filling materials. An investigation by neutron activation analysis. Acta Pharmacol Toxicol Suppl 59:56-59.

*Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokinet 5(6):485-527.

Müller J. 1985. Atmospheric pathways of heavy metals. Proc Heavy Metal Environ Int Conf 1:214-216.

Mumma RO, Raupach DC, Waldman JP, et al. 1984. National survey of elements and other constituents in municipal sewage sludge. Arch Environ Contam Toxicol 13:75-83.

*Muramatsu Y, Parr RM. 1988. Concentrations of some trace elements in hair, liver and kidney from autopsy subjects - relationship between hair and internal organs. Sci Total Environ 76:29-40.

*Murrell NE. 1987. Impact of metallic solders on water quality. Proc Am Water Works Assoc 1987(Pt. 1):39-43.

+*Myers RC, Homan ER, Well CS, et al. 1978. Antimony trioxide range-finding toxicity studies. Carnegie-Mellon Institute of Research, Carnegie-Mellon University, Pittsburgh, PA, sponsored by Union Carbide. OTS206062.

*Nakamaru YM, Sekine K. 2008. Sorption behavior of selenium and antimony in soils as a function of phosphate ion concentration. Soil Sci Plant Nutr 54(3):332-341. 10.1111/j.1747-0765.2008.00247.x.

9. REFERENCES

*NAS/NRC. 1989. Report of the oversight committee. Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press, 15-35.

*Neves DB, Caldas ED, Sampaio RN. 2009. Antimony in plasma and skin of patients with cutaneous leishmaniasis--relationship with side effects after treatment with meglumine antimoniate. Trop Med Int Health 14(12):1515-1522. 10.1111/j.1365-3156.2009.02408.x.

+*Newton PE, Bolte HF, Daly IW, et al. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol 22(4):561-576.

Nightingale HI. 1987. Water quality beneath urban runoff water management basins. Water Resource Bull 23:197-205.

NIOSH. 1981. Occupational health guidelines for chemical hazards. U.S. Department of Health and Human Services. National Institute for Occupational Safety and Health.

*NIOSH. 1985. Method 8005. Elements in blood or tissue. Cincinnati, OH: Division of Physical Sciences and Engineering, National Institute for Occupational Safety and Health.

*NIOSH. 1987. Method 6008. Stibine. Manual of analytical methods: Cincinnati, OH: Division of Physical Sciences and Engineering, National Institute for Occupational Safety and Health, 6008-l to 6008-4.

*NIOSH. 1989. National Occupational Exposure Survey (NOES). Washington, DC: National Institute for Occupational Safety and Health. March 29, 1989.

NIOSH: 1990. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

*NIOSH. 2015a. Antimony. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/npgd0036.html. November 9, 2015.

*NIOSH. 2015b. Stibine. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention. http://www.cdc.gov/niosh/npg/npgd0568.html. November 9, 2015.

*NRC. 1993. Pesticides in the diets of infants and children. Washington, DC: National Research Council. National Academy Press. PB93216091.

*Nriagu JO. 1989. A global assessment of natural sources of atmospheric trace metals. Nature 338:47-49.

NTP. 1990. National Toxicology Program. Technical report on the toxicity studies of antimony potassium tartrate in F344/N rats, and B6C3Fl mice (dosed water and intraperitoneal injection studies). Draft (NTPTOX 11). Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health.

9. REFERENCES

+*NTP. 1992. NTP report on the toxicity studies of antimony potassium tartrate in F344/N rats and B6C3F$_1$ mice (drinking water and intraperitoneal injection studies). Research Triangle Park, NC: NTP Tox 11. NIH Publication No. 92-3130.

*NTP. 2013. Draft OHAT approach for systematic review and evidence integration for literature-based health assessments- February 2013. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation. https://ntp.niehs.nih.gov/ntp/ohat/evaluationprocess/draftohatapproach_february2013.pdf. April 13, 2016

*NTP. 2014. Report on carcinogens. Thirteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. http://ntp.niehs.nih.gov/pubhealth/roc/roc13/. April 9, 2015.

*NTP. 2015. Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. National Toxicology Program, U.S. Department of Health and Human Services, Office of Health Assessment and Translation. http://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf. October 2, 2015.

+*NTP. 2016. NTP technical report on the toxicology and carcinogenesis studies of antimony trioxide (CAS No. 1309-64-4) in Wistar Han [Crl:WI (Han)] rats and B6C3F1/N mice. NTP TR 590.

*Ohmori S, Tsuji H, Kusaka Y, et al. 1981. Radioactivation analysis of hair. A means of biological monitoring of the environment. J Radioanal Chem 63:269-282.

Olmez I, Gulovali MC, Gordon GE. 1978. Trace substances in human saliva. Environ Health 7:231-240.

*Olmez I, Kotra JP, Lowery S, et al. 1985. Airborne lead and trace elements in an indoor shooting range: A study of the DC National Guard Armory Pistol Range. Environ Toxicol Chem 4:447-452.

+*Omura M, Tanaka A, Hirata M, et al. 2002. Testicular toxicity evaluation of two antimony compounds, antimony trioxide and antimony potassium tartrate, in rats and mice. Environ Health Prev Med 7(1):15-18. 10.1007/bf02898061.

OSHA. 1989. U.S. Department of Labor. Occupational Safety and Health Administration. OSHA occupational standards permissible exposure limits. 29 CFR 1910.1000. Fed Regist 54:2924.

*OSHA. 2013. Subpart Z - Toxic and hazardous substances. Air contaminants. Code of Federal Regulations. Occupational Safety and Health Standards. 29 CFR 1910.1000. http://www.gpo.gov/fdsys/pkg/CFR-2014-title29-vol6/pdf/CFR-2014-title29-vol6-sec1910-1000.pdf. March 4, 2015.

*OSHA. 2014. Subpart Z - Toxic and hazardous substances. Air contaminants. Table Z - Shipyards. Code of Federal Regulations. Occupational Safety and Health Standards. 29 CFR 1915.1000. http://www.gpo.gov/fdsys/pkg/CFR-2013-title29-vol7/pdf/CFR-2013-title29-vol7-sec1915-1000.pdf. March 4, 2015.

*Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

*Paßlack N, Mainzer B, Lahrssen-Wiederholt M, et al. 2014a. Concentrations of strontium, barium, cadmium, copper, zinc, manganese, chromium, antimony, selenium and lead in the equine liver and kidneys. SpringerPlus 3:343. 10.1186/2193-1801-3-343.

*Paßlack N, Mainzer B, Lahrssen-Wiederholt M, et al. 2014b. Concentrations of strontium, barium, cadmium, copper, zinc, manganese, chromium, antimony, selenium and lead in the liver and kidneys of dogs, depending on age, sex and the occurrence of a chronic kidney disease. J Vet Sci 16(1):57-66.

*Paßlack N, Mainzer B, Lahrssen-Wiederholt M, et al. 2014c. Liver and kidney concentrations of strontium, barium, cadmium, copper, zinc, manganese, chromium, antimony, selenium and lead in cats. BMC Vet Res 10:163. 10.1186/1746-6148-10-163.

Pacyna JM. 1984. Estimation of the atmospheric emissions of trace elements from anthropogenic sources in Europe. Atmos Environ 18:41-50.

*Pacyna JM, Pacyna EG. 2001. An assessment of global and regional emissions of trace metals to the atmosphere from anthropogenic sources worldwide. NRC Research Press. Environ Rev 9(4):269-298. 10.1139/a01-012. http://www.nrcresearchpress.com/doi/abs/10.1139/a01-012. 2016/03/17.

*Pacyna JM, Semb A, Hanssen JE. 1984. Emission and long-range transport of trace elements in Europe. Tellus Ser B 36B:163-178.

+*Palacios N, Fitzgerald K, Roberts AL, et al. 2014. A prospective analysis of airborne metal exposures and risk of Parkinson disease in the nurses' health study cohort. Environ Health Perspect 122(9):933-938. 10.1289/ehp.1307218.

*Palacios R, Osorio LE, Grajales LF, et al. 2001. Treatment failure in children in a randomized clinical trial with 10 and 20 days of meglumine antimonate for cutaneous leishmaniasis due to *Leishmania Viannia* species. Am J Trop Med Hyg 64(3-4):187-193.

*Pan X, Zhang D, Chen X, et al. 2010. Antimony accumulation, growth performance, antioxidant defense system and photosynthesis of *Zea mays* in response to antimony pollution in soil. Water Air Soil Pollut 215(1):517-523. 10.1007/s11270-010-0496-8.

*Pandey AK, Kumar M, Thakur CP. 1988. EGG changes in prolonged treatment of kalazar with antimony compounds [letter]. J Assoc Physicians India 36:398-399.

Papastefanou C, Manolopoulou M, Sawidis T. 1988. Lichens and mosses: Biological monitors of radioactive fallout from the Chernobyl Reactor accident. J Environ Radioactivity 9:199-207.

Parris GE, Brinckman FE. 1975. Reactions which relate to the environmental mobility of arsenic and antimony. I. Quarternization of trimethylarsine and trimethylstibine. J Org Chem 40:3801-3803.

Parris GE, Brinckman FE. 1976. Reactions which relate to environmental mobility of arsenic and antimony. II. Oxidation of trimethylarsine and trimethylstilbene. Environ Sci Technol 10:1128-1134.

*Paton GR, Allison AC. 1972. Chromosome damage in human cell cultures induced by metal salts. Mutat Res 16:332-336.

*Pattenden NJ, Branson JR, Fisher EMR. 1982. Trace element measurements in wet and dry deposition and airborne particulate at an urban site. Deposition Atmos Pollut Proc Collog 173-184.

*Perez-Corona T, Madrid Y, Camara C. 1997. Evaluation of selective uptake of selenium (Se(IV) and Se(VI)) and antimony (Sb(III) and Sb(V)) species by baker's yeast cells (*Saccharomyces cerevisiae*). Anal Chim Acta 345(1-3):249-255.

*Plunkert PA. 1982. Antimony. In: Minerals handbook. Pittsburgh, PA: Bureau of Mines, U.S. Department of the Interior, 93-101.

+*Poon R, Chu I, Lecavalier P, et al. 1998. Effects of antimony on rats following 90-day exposure via drinking water. Food Chem Toxicol 36(1):21-35.

+*Potkonjak V, Pavlovich M. 1983. Antimoniosis: A particular form of pneumoconiosis. I. Etiology, clinical and x-ray findings. Int Arch Occup Environ Health 51:199-207.

*Potkonjak V, Vishnjich V. 1983. Antimoniosis: A particular form of pneumoconiosis. II. Experimental investigation. Int Arch Occup Environ Health 51:299-303.

Pradeau D, Petiot J, Bissery V, et al. 1988. Study on the transfer of inorganic elements from glass to solvents in pharmaceutical use. Int Pharm J 2:209-215.

+*Price NH, Yates WG, Allen SD. 1979. Toxicity evaluation for establishing IDLH values. Cincinnati, OH: National Institute for Occupational Safety and Health. PB87-229498.

*Quiroz W, Arias H, Bravo M, et al. 2011. Development of analytical method for determination of Sb(V), Sb(III) and TMSb(V) in occupationally exposed human urine samples by HPLC-HG-AFS. Microchem J 97(1):78-84.

*Ragaini RC, Ralston HR, Roberts N. 1977. Environmental trace metal contamination in Kellogg, Idaho near a lead smelting complex. Environ Sci Technol 11:773-781.

Rai D, Zachara JM, Schwab AP, et al. 1984. Chemical attenuation rates, coefficients, and constants in leachate migration. Volume 1: A critical review. Electric Power Research Institute Publication EPRI EA-3356.

Rawlings GD. 1980. Analysis of priority pollutants at a primary aluminum production facility. Environ Int 3:321-325.

*Rees PH, Keating MI, Kager PA, et al. 1980. Renal clearance of pentavalent antimony (sodium stibogluconate). Lancet 2:226-229.

+*Renes LE. 1953. Antimony poisoning in industry. Arch Ind Hyg 7:99-108.

*RePORTER. 2015. Antimony. National Institutes of Health, Research Portfolio Online Reporting Tools. http://projectreporter.nih.gov/reporter.cfm. November 4, 2016.

*Ribeiro RR, Ferreira WA, Martins PS, et al. 2010. Prolonged absorption of antimony(V) by the oral route from non-inclusion meglumine antimoniate-beta-cyclodextrin conjugates. Biopharm Drug Dispos 31(2-3):109-119. 10.1002/bdd.695.

*Richardson BA. 1994. Sudden infant death syndrome: a possible primary cause. J Forensic Sci Soc 34(3):199-204.

*Rooney AA, Boyles AL, Wolfe MS, et al. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122(7):711-718. 10.1289/ehp.1307972.

+*Rossi F, Acampora R, Vacca C, et al. 1987. Prenatal and postnatal antimony exposure in rats: Effect on vasomotor reactivity development of pups. Teratogen Carcinogen Mutagen 7:491-496.

Rossmann R. 1988. Estimation of trace metal storage in Lake St. Clair post-settlement sediments using composite samples. J Great Lakes Res 14:66-75.

*RTECS. 2015. Antimony and compounds. Registry of Toxic Effects on Chemical Substances. National Institute of Occupational Safety and Health. MDL Information Systems, Inc. June 2, 2015.

Rugemalila JB. 1980. Fatal stibocaptate toxicity. East Afr Med J 57:720-722.

Sabbioni E, Goetz L, Bignoli G. 1984. Health and environmental implications of trace metals released from coal-fired power plants: An assessment study of the situation in the European community. Sci Total Environ 40:141-154.

Sabbioni E, Goetz L, Springer A, et al. 1983. Trace metals from coal-fired power plants: Derivation of an average data base for assessment studies of the situation in the European communities. Sci Total Environ 29:213-227.

Salisbury SA. 1980. Health hazard evaluation no ME-79-075-784 at St. Clair Rubber Company, Marysville, Michigan. Cincinnati, OH: Hazard Evaluations and Technical Assistance Branch, Division of Surveillance Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health.

*Sarkis JE, Neto ON, Viebig S, et al. 2007. Measurements of gunshot residues by sector field inductively coupled plasma mass spectrometry-further studies with pistols. Forensic Sci Int 172(1):63-66. 10.1016/j.forsciint.2006.12.007.

*Saunders NR, Ek CJ, Habgood MD, et al. 2008. Barriers in the brain: A renaissance? Trends Neurosci 31(6):279-286. 10.1016/j.tins.2008.03.003.

*Saunders NR, Liddelow SA, Dziegielewska KM. 2012. Barrier mechanisms in the developing brain. Front Pharmacol 3:Article 46. 10.3389/fphar.2012.00046.

*Schaumlöffel N, Gebel T. 1998. Heterogeneity of the DNA damage provoked by antimony and arsenic. Mutagenesis 13(3):281-286.

*Scheinost AC, Rossberg A, Vantelon D, et al. 2006. Quantitative antimony speciation in shooting-range soils by EXAFS spectroscopy. Geochim Cosmochim Acta 70(13):3299-3312.

*Scheuplein R, Charnley G, Dourson M. 2002. Differential sensitivity of children and adults to chemical toxicity. I. Biological basis. Regul Toxicol Pharmacol 35(3):429-447.

+*Schnorr TM, Steenland K, Thun MJ, et al. 1995. Mortality in a cohort of antimony smelter workers. Am J Ind Med 27(5):759-770.

*Schonwald S. 2004. Antimony. In: Dart RC, ed. Medical toxicology. Philadelphia, PA: Lippincott Williams & Wilkins, 1391-1392.

Schroeder HA, Mitchener M, Balassa JJ, et al. 1968. Zirconium, niobium, antimony, and fluorine in mice: Effects on growth, survival and tissue levels. J Nutr 95:95-101.

+*Schroeder HA, Mitchener M, Nason AP. 1970. Zirconium, niobium, antimony, vanadium and lead in rats: Life-time studies. J Nutr 100:59-68.

*Shacklette HT, Boerngen JG. 1984. Element concentration in soils and other surficial materials of the conterminous United States. U.S. Geological Survey Professional Paper 1270. Alexandria VA: U.S. Geological Survey.

*Shannon MW, Borron SW, Burns MJ. 2007. Antimony. In: Haddad and Winchester's clinical management of poisoning and drug overdose. Philadelphia, PA: Saunders Elsevier, 917, 1158.

+Shirai S, Suzuki Y, Yoshinaga J, et al. 2010. Maternal exposure to low-level heavy metals during pregnancy and birth size. J Environ Sci Health A Tox Hazard Subst Environ Eng 45:1468-1474. 10.1080/10934529.2010.500942.

+*Shiue I. 2014. Higher urinary heavy metal, arsenic, and phthalate concentrations in people with high blood pressure: US NHANES, 2009-2010. Int J Environ Res Public Health 11(6):5989-5999. 10.3109/08037051.2014.925228.

+*Shiue I. 2015. Relationship of environmental exposures and ankylosing spondylitis and spinal mobility: US NHANES, 2009-2010. Int J Environ Health Res 25(3):322-329. 10.1080/09603123.2014.945512.

+*Shiue I, Hristova K. 2014. Higher urinary heavy metal, phthalate and arsenic concentrations accounted for 3-19% of the population attributable risk for high blood pressure: US NHANES, 2009-2012. Hypertens Res 37(12):1075-1081. 10.1038/hr.2014.121.

Small M, Germani MS, Small AM, et al. 1981. Airborne plume study of emissions from the processing of copper ores in southeastern Arizona. Environ Sci Technol 15:293-299.

*Smichowski P. 2008. Antimony in the environment as a global pollutant: A review on analytical methodologies for its determination in atmospheric aerosols. Talanta 75(1):2-14. 10.1016/j.talanta.2007.11.005.

*Smith MM, White MA, Wilson HK. 1995. Determination of antimony in urine by solvent extraction and electrothermal atomization atomic absorption spectrometry for the biological monitoring of occupational exposure. J Anal Atom Spectrom 10(6):349-352.

+*Smyth HF, Carpenter CP. 1948. Further experience with the range finding test in the industrial toxicology laboratory. J Ind Hyg Toxicol 30:63-68.

+*Smyth HF, Thompson WL. 1945. The single dose and subacute-toxicity of antimony oxide (SB_2O_3). Melon Institute of Industrial Research, University of Pittsburgh. OTS206062.

*Stauffer RE, Thompson JM. 1984. Arsenic and antimony in geothermal waters of Yellowstone National Park, Wyoming, USA. Geochim Cosmochim Acta 48(12):2547-2561.

+*Stevenson CJ. 1965. Antimony spots. Transactions of the St. John's Hospital Dermatology Society, 51:40-42.

*Stoessel RP, Michaelis W. 1986. Wet and dry deposition of heavy metals. In: Proceedings of the 2nd Environmental Contamination International Conference, 85-88.

Strohal P, Huljer D, Lubic S, et al. 1975. Antimony in the coastal marine environment, North Adriatic. Estuarine Coastal Marine Sci 3:119-123.

*Sturgeon RE, Willie SN, Berman SS. 1985. Preconcentration of selenium and antimony from seawater for determination by graphite furnace atomic absorption spectrometry. Anal Chem 57:6-9.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 206-207.

*Sumino K, Hayakawa K, Shibata T, et al. 1975. Heavy metals in normal Japanese tissues. Arch Environ Health 30:487-494.

*Sun H, Yan SC, Cheng WS. 2000. Interaction of antimony tartrate with the tripeptide glutathione implication for its mode of action. Eur J Biochem 267(17):5450-5457.

+*Sunagawa S. 1981. Experimental studies on antimony poisoning. Igaku kenkyu 51:129-142.

*Sundar S, Sinha PR, Agrawal NK, et al. 1998. A cluster of cases of severe cardiotoxicity among kala-azar patients treated with a high-osmolarity lot of sodium antimony gluconate. Am J Trop Med Hyg 59(1):139-143.

Sutker BJ. 1988. Fire retardants. In: Ullmann's encyclopedia of industrial chemistry. 5th ed. Free Republic of Germany: VCH Vereagegeselschaft Weinheim, 136-137.

Swellengrebel NH, Sterman MM. 1961. Animal parasites in man. Princeton, NJ: D. Van Nostrand Co., Inc., 178-180.

*Takagi Y, Matsuda S, Imai S, et al. 1986. Trace elements in human hair: An international comparison. Bull Environ Contam Toxicol 36:793-800.

*Takagi Y, Matsuda S, Imai Y, et al. 1988. Survey of trace elements in human nails: An international comparison. Bull Environ Contam Toxicol 41:690-695.

Tanner JT, Friedman MH. 1977. Neutron activation analysis for trace elements in foods. J Radioanal Chem 37:529.

*Tarabar AF. 2014. Antimony. In: Goldfrank's toxicologic emergencies. 10th ed. New York, NY: McGraw-Hill Education, 1161-1167.

*Taylor PJ. 1966. Acute intoxication from antimony trichloride. Br J Ind Med 23:318-321.

*Telford K, Maher W, Krikowa F, et al. 2008. Measurement of total antimony and antimony species in mine contaminated soils by ICPMS and HPLC-ICPMS. J Environ Monit 10(1):136-140. 10.1039/b715465h.

*Thakur CP. 1998. Sodium antimony gluconate, amphotericin, and myocardial damage. Lancet 351(9120):1928-1929.

*Thomas K, Colborn T. 1992. Organochlorine endocrine disruptors in human tissue. In: Colborn T, Clement C, eds. Chemically induced alterations in sexual and functional development: The wildlife/human connection. Princeton, NJ: Princeton Scientific Publishing, 365-394.

*Thomas RG, Felicetti SW, Lucchino RV, et al. 1973. Retention patterns of antimony in mice following inhalation of particles formed at different temperatures. Proc Exp Biol Med 144:544-550.

*Tirmenstein MA, Mathias PI, Snawder JE, et al. 1997. Antimony-induced alterations in thiol homeostasis and adenine nucleotide status in cultured cardiac myocytes. Toxicology 119(3):203-211.

*Tirmenstein MA, Plews PI, Walker CV, et al. 1995. Antimony-induced oxidative stress and toxicity in cultured cardiac myocytes. Toxicol Appl Pharmacol 130(1):41-47. 10.1006/taap.1995.1006.

*Toraason M, Wey HE, Richards DE, et al. 1997. Altered Ca2+ Mobilization during excitation contraction in cultured cardiac myocytes exposed to antimony. Toxicol Appl Pharmacol 146(1):104-115.

*TRI14 2016. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. March 22, 2016.

Trnovsky M, Oxer JP, Rudy RJ, et al. 1988. Site remediation of heavy metals contaminated soils and groundwater at a former battery reclamation site in Florida. In: Proceedings of the Hazardous Waste: Detection, Control, and Treatment World Conference, Pt. B, 1581-1590.

*Tschan M, Robinson B, Schulin R. 2008. Antimony uptake by *Zea mays* (L.) and *Helianthus annuus* (L.) from nutrient solution. Environ Geochem Health 30(2):187-191. 10.1007/s10653-008-9142-4.

*Tschan M, Robinson BH, Schulin R. 2009. Antimony in the soil–plant system – a review. Huanjing Huaxue 6(2):106-115. 10.1071/EN08111.

*Tu AS, Sivak A. 1984. Evaluation of antimony thioantimonate in three *in vitro* short-term assays. Wright-Patterson Air Force Base, OH: U.S. Air Force Aerospace Medical Research Laboratory. ADA150348.

*U.S. Bureau of Mines. 1989. Antimony in the 2nd quarter of 1989. Mineral Industry Series. U.S. Bureau of Mines, Pittsburgh, PA. August 23, 1989.

*USGS. 2004. Mineral commodity profiles. Antimony. U.S. Geological Survey. Open-File Report 03-019. http://pubs.usgs.gov/of/2003/of03-019/of03-019.pdf. March 17, 2016.

*USGS. 2010. Water-chemistry data for selected springs, geysers, and streams in Yellowstone National Park, Wyoming, 2006-2008. U.S. Department of the Interior, U.S. Geological Survey. Open-File Report 2010-1192. Water-chemistry data for selected springs, geysers, and streams in Yellowstone National Park, Wyoming, 2006-2008. March 15, 2016.

9. REFERENCES

*USGS. 2011. National water-quality assessment program. Trace elements and radon in groundwater across the United States, 1992-2003. U.S. Department of the Interior, U.S. Geological Survey. Scientific Investigations Report 2011-5059. http://pubs.usgs.gov/sir/2011/5059/pdf/sir2011-5059_report-covers_508.pdf. March 22, 2016.

*USGS. 2015. Mineral industry surveys. Antimony in the fourth quarter 2014. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/antimony/mis-2014q4-antim.pdf. March 17, 2016.

*Vandecasteele C, Vermeir G, Dams R. 1988. Element concentrations in the air of an indoor shooting range. Environ Technol Lett 9:1287-1294.

Van der Sloot HA, Wijkstra J, Van Dalen A, et al. 1982. Leaching of trace elements from coal solid waste. Netherlands Energy Research Foundation, ECN, Petten. ECN-120.

*Van Velzen D, Langenkamp H, Herb G. 1998. Antimony, its sources, applications and flow paths into urban and industrial waste: A review. Waste Manag Res 16(1):32-40.

*Vasquez L, Scorza Dagert JV, Scorza JV, et al. 2006. Pharmacokinetics of experimental pentavalent antimony after intramuscular administration in adult volunteers. Curr Ther Res Clin Exp 67(3):193-203. 10.1016/j.curtheres.2006.06.005.

*Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238(2):476-483.

*Vinas P, Lopez-Garcia I, Merino-Merono B, et al. 2006. Liquid chromatography-hydride generation-atomic fluorescence spectrometry hybridation for antimony speciation in environmental samples. Talanta 68(4):1401-1405. 10.1016/j.talanta.2005.07.056.

*Vong RJ, Larson TV, Zoller WH. 1988. A multivariate chemical classification of rainwater samples. Chemom Intel1 Lab Syst 3:99-109.

Von Gunten HR, Ku11 TP. 1986. Infiltration of inorganic compounds from the Glatt River, Switzerland, into a groundwater aquifer. Water Air Soil Pollut 29:333-346.

Warren CJ, Dudas M.J. 1988. Leaching behavior of selected trace elements in chemically weathered alkaline fly ash. Sci Total Environ 76:229-246.

*Watt WD. 1980. Chronic inhalation toxicity of antimony trioxide: Validation of the T.L.V. Progress report-summary of results. OTS206195.

+*Watt WD. 1983. Chronic inhalation toxicity of antimony trioxide: Validation of the threshold limit value. Dissertation, Wayne State University.

*Weast RC. 1988. Handbook of chemistry and physics. 69th ed. Boca Raton, FL: CRC Press, B-8, B-72 to B-73.

Webber MD, Shamess A. 1987. Heavy metal concentrations in Halton Region soils: An assessment for future municipal sludge utilization. Can J Soil Sci 67:893-903.

*West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

Westrick ML. 1953. Physiologic responses attending administration of antimony, alone or with simultaneous injections of thyroxin. Proc Soc Exp Biol Med 82:56-60.

*Wey HE, Richards D, Tirmenstein MA, et al. 1997. The role of intracellular in antimony-induced toxicity in cultured cardiac myocytes. Toxicol Appl Pharmacol 145(1):202-210.

*WHO. 2003. Antimony in drinking-water. World Health Organization. http://www.who.int/water_sanitation_health/dwq/chemicals/antimony.pdf. March 15, 2016.

*WHO. 2010. WHO guidelines for indoor air quality: Selected pollutants. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. September 9, 2014.

*WHO. 2011. Guidelines for drinking-water quality. Geneva, Switzerland: World Health Organization. http://whqlibdoc.who.int/publications/2011/9789241548151_eng.pdf?ua=1. September 9, 2014.

*Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advance treatise. Volume II: The elements Part A. New York, NY: Academic Press, 1-247.

*Wiersema JM, Wright L, Rogers B, et al. 1984. Human exposure to potentially toxic elements through ambient air in Texas. Proc Air Pollut Contr Assoc 1:84-1.2.

Wil Research Laboratories, Inc. 1979. Acute eye irritation study in rabbits with antimony oxide. Sponsored by PPG Industries Inc., Pittsburgh, PA.

Willetts P, Anderson RA, Farmer JG, et al. 1982. Inorganic elements in the tracheas of fire fatalities. Fire Mater 6:32-37.

*Wilson SC, Lockwood PV, Ashley PM, et al. 2010. The chemistry and behaviour of antimony in the soil environment with comparisons to arsenic: A critical review. Environ Pollut 158(5):1169-1181. 10.1016/j.envpol.2009.10.045.

*Windholz M, ed. 1983. The Merck index. 10th ed. Rahway, NJ: Merck and Co., 102-104.

Woessner WM, Shapley. 1985. Effects of U.S. antimony's disposal ponds on an alluvial aquifer and Prospect Creek, western Montana.

*Wong LCK, Winston JM, Hagensen J, et al. 1979. Study of carcinogenicity and toxicity of inhaled antimony trioxide, antimony ore concentrate and thallic oxide in rats. Cincinnati, OH: National Institute for Occupational Safety and Health, U.S. Department of Health. OTS0511065.

Yocom JE. 1983. Industrial sources of metals. NeuroToxicology 4:91-102.

Young M. 1979a. Walk-through survey report of General Battery and Ceramic Corporation, Dallas, Texas. Cincinnati, OH: Division of Surveillance, Hazard Evaluations, and Field Studies, Industry-wide Studies Branch, Industrial Hygiene Section, National Institute for Occupational Safety and Health.

Young M. 1979b. Walk-through survey report of Standard Industries, Inc. (Reliable Battery Company), San Antonio, Texas. Cincinnati, OH: Division of Surveillance, Hazard Evaluations, and Field Studies, Industry-wide Studies Branch, Industrial Hygiene Section, National Institute for Occupational Safety and Health.

Young M, Beaumont J, Brown D, et al. 1979. Walk-through survey report of Electric Storage Battery, Inc., Dallas, Texas. Cincinnati, OH: Division of Surveillance, Hazard Evaluations, and Field Studies, Industry-wide Studies Branch, Industrial Hygiene Section, National Institute for Occupational Safety and Health.

*Yu RC, Rappaport SM. 1996. Relation between pulmonary clearance and particle burden: A Michaelis-Menten-like kinetic model. Occup Environ Med 53(8):567-572.

*Zaki MH, Shookhoff HB, Sterman M, et al. 1964. Astiban in *Schistosomiasis mansoni*: A controlled therapeutic trial in a nonendemic area. Am J Trop Med Hyg 13:803-810.

Zhang J, Billiet J, Dams R. 1985. Elemental composition and source investigation of particulates suspended in the air of an iron foundry. Sci Total Environ 41:13-28.

+*Zheng FY, Qian SH, Li SX, et al. 2006. Speciation of antimony by preconcentration of Sb(III) and Sb(V) in water samples onto nanometer-size titanium dioxide and selective determination by flow injection-hydride generation-atomic absorption spectrometry. Anal Sci 22(10):1319-1322.

*Zheng G, Zhong H, Guo Z, et al. 2014. Levels of heavy metals and trace elements in umbilical cord blood and the risk of adverse pregnancy outcomes: A population-based study. Biol Trace Elem Res 160(3):437-444. 10.1007/s12011-014-0057-x.

*Zeiger E, Anderson B, Haworth S, et al. 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ Mol Mutagen 21:2-141.

*Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12(1):29-34.

*Zikovsky L, Badillo M. 1987. An indirect study of air pollution by neutron activation analysis of snow. J Radioanal Nucl Chem 114:147-153.

9. REFERENCES

This page is intentionally blank.

10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study— A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Antimony
CAS Numbers: 7440-36-0
Date: April 2017
Profile Status: Draft for Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 5
Species: Mice

Minimal Risk Level: 0.001 [ ] mg/kg/day [X] mg Sb/m^3

Reference: NTP. 2016. Toxicology and carcinogenicity studies of antimony trioxide (CAS No. 1309-64-4) in Wistar HAN [Crl:WI (Han)] rats and B6C3F1/N mice (inhalation studies). National Toxicology Program, Research Triangle Park, NC. NTP TR 590. Draft for Peer Review.

Experimental design: Groups of five male and five female B6C3F1/N mice were exposed to 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 antimony trioxide (0, 3.1, 6.3, 12, 25, and 50 mg Sb/m^3) 6 hours/day, 5 days/week for 13 exposures in a 17-day period. An additional group of five female mice was similarly exposed and held for a 28-day recovery period. The actual concentrations were 3.71, 7.43, 14.7, 30.2, and 59.4 mg Sb_2O_3/m^3. The MMADs (geometric standard deviations) for the particles were 1.4 (1.9), 1.3 (1.9), 1.5 (1.9), 1.4 (1.9), and 1.4 (1.9) μm for the 3.1, 6.3, 12, 25, and 50 mg Sb/m^3 concentrations, respectively. The following parameters were used to assess toxicity: twice daily observations; body weights on days 1, 6, 13, and at termination; organ weights (kidney, liver, lung, testis, thymus); and histopathological examination in the control and 50 mg Sb/m^3 group (histopathological examinations of the larynx, lung, lymph nodes, nose, pharynx, and trachea were conducted to a no-effect level). In the animals allowed to recover, antimony levels were measured in blood samples collected at the end of the exposure and recovery periods and in the lungs.

Although the mice were exposed to antimony trioxide over a 17-day period, the animals were only exposed for 13 times and the study was considered to more reflective of effects associated with acute-duration exposure than intermediate-duration exposure.

Effect noted in study and corresponding doses: No deaths, clinical findings, or alterations in body weight gain were observed. Significant increases in absolute lung weights were observed in males at ≥6.3 mg Sb/m^3 and in females at ≥12 mg Sb/m^3; increases in relative lung weights were observed in males at 50 mg Sb/m^3 and in females at ≥3.1 mg Sb/m^3. Minimal to mild squamous metaplasia was observed in the epiglottis epithelium at ≥25 mg Sb/m^3; the incidences were 0/10 in controls and 2/10, 4/9, 10/10, and 10/10 in the 6.3, 12, 25, and 50 mg Sb/m^3 groups, respectively. Increases in the presence of foreign body (presumably antimony trioxide) were observed in the lungs of mice exposed to ≥3.1 mg Sb/m^3. No concentration-related alterations in lung clearance were observed. The clearance half-times ranged from 47 to 62 days.

Dose and end point used for MRL derivation: The MRL is based on a $BMCL_{10}$ of 0.94 mg Sb/m^3 for squamous metaplasia of the epiglottis in male and female mice.

[ ] NOAEL [ ] LOAEL [X] $BMCL_{10}$

Several end points were considered for derivation of an acute-duration inhalation MRL for antimony: altered EKGs and degenerative changes in the heart in rabbits exposed to 19.9 mg Sb/m^3 as antimony

trisulfide (Brieger et al. 1954), lung inflammation in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide (Brieger et al. 1954), squamous metaplasia of the epiglottis in male and female rats exposed to ≥25 mg Sb/m^3 as antimony trioxide (NTP 2016), chronic lung inflammation in rats exposed to ≥25 mg Sb/m^3 as antimony trioxide (NTP 2016), and squamous metaplasia of the epiglottis in male and female mice exposed to ≥12 mg Sb/m^3 as antimony trioxide (NTP 2016).

For the NTP (2016) study, the incidence data (Table A-1) for squamous metaplasia in rats and mice were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For all lesion types, a BMR of 10% was used. Since the response level for chronic inflammation was the same for all non-control concentrations (see Table A-1), BMD modeling was not conducted for this end point and the NOAEL was used as the POD. The model predictions for the epiglottal squamous metaplasia for rats and mice are presented in Tables A-2 and A-3 and the fits of the selected models are presented in Figures A-1 and A-2. The Brieger et al. (1954) study only tested one concentration of antimony trisulfide, and was not considered suitable for BMD modeling; the LOAEL of 19.9 mg Sb/m^3 for lung and cardiovascular effects was considered the POD for this study.

Table A-1. Incidence of Respiratory Tract Effects in Male and Female Rats and Mice Exposed to Antimony Trioxide (NTP 2016)[a]

	Concentrations (mg Sb/m^3)					
Effect	0	3.1	6.3	12	25	50
Rats						
Squamous metaplasia of epiglottis	0/10	–[b]	–[b]	1/10	4/9[c]	5/10[c]
Chronic lung inflammation	0/10	0/10	0/10	0/10	10/10[c]	10/10[b]
Mice						
Squamous metaplasia of epiglottis (male and female)	0/10	–[d]	2/10	4/9[c]	10/10[c]	10/10[c]

[a]Male and female incidences were combined.
[b]Incidence in the female rats was 1/5; males were not examined at these concentrations.
[c]Significantly different from controls.
[d]Incidence in the female mice was 2/5; males were not examined at this concentration.

Table A-2. Model Predictions for the Incidence of Squamous Metaplasia of the Epiglottis in Male and Female Rats (Combined) Exposed to Antimony Trioxide (NTP 2016)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	2	1.04	0.60	0.00	-0.49	0.83	37.76	7.77	4.18
Logistic	2	3.09	0.21	-0.28	1.41	1.41	40.25	16.36	10.83
LogLogistic[d,e]	***2***	***0.90***	***0.64***	***0.00***	***-0.46***	***0.75***	***37.62***	***8.47***	***2.95***
LogProbit[d]	3	0.99	0.80	0.00	-0.16	0.78	35.68	10.99	7.27
Multistage (1-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Multistage (2-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Multistage (3-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Probit	2	2.86	0.24	-0.22	1.38	1.38	39.91	15.35	10.31
Weibull[c]	2	1.04	0.59	0.00	-0.53	0.82	37.77	7.40	4.17

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Log Logistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-1. Fit of LogLogistic Model to Data on Incidence of Epiglottal Squamous Metaplasia in Male and Female Rats Exposed to Antimony Trioxide (mg Sb/m^3)

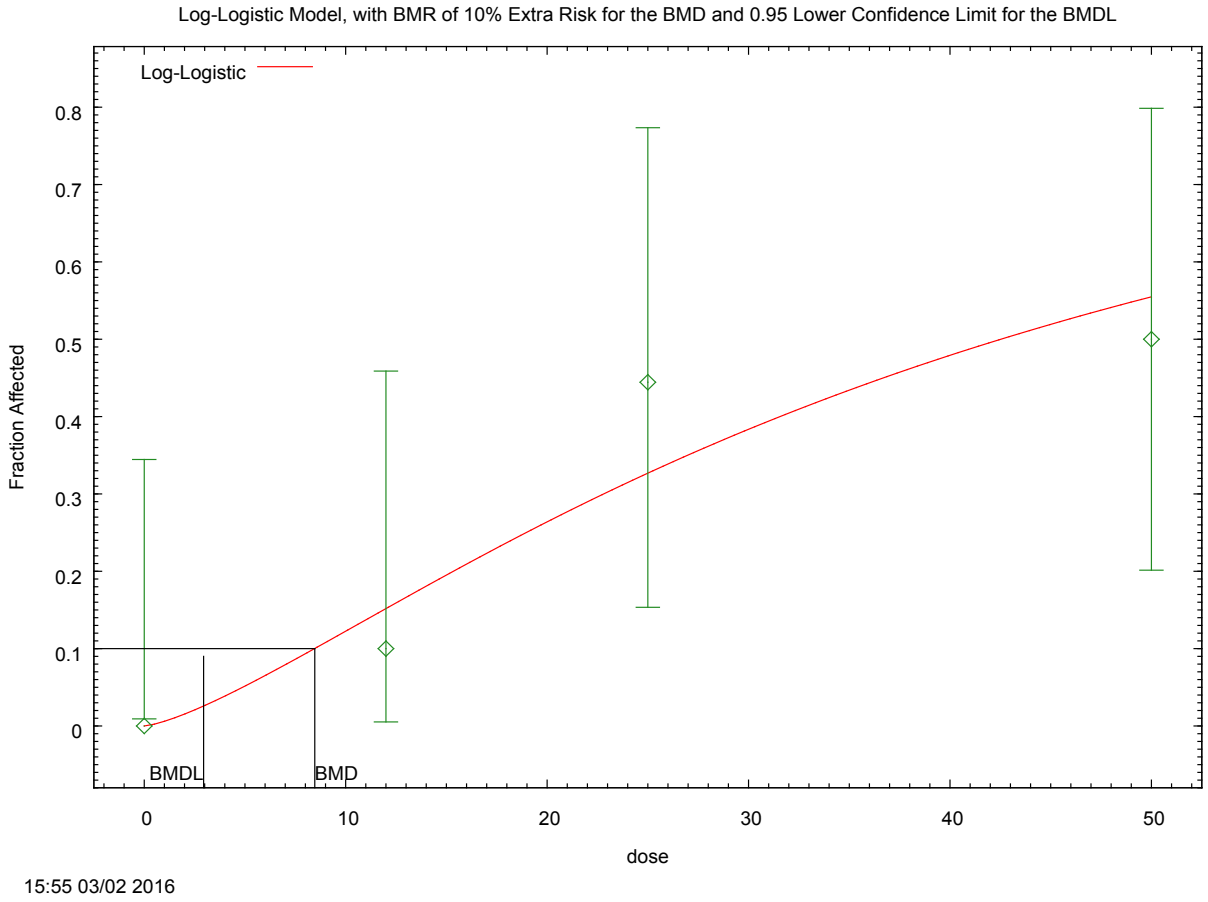


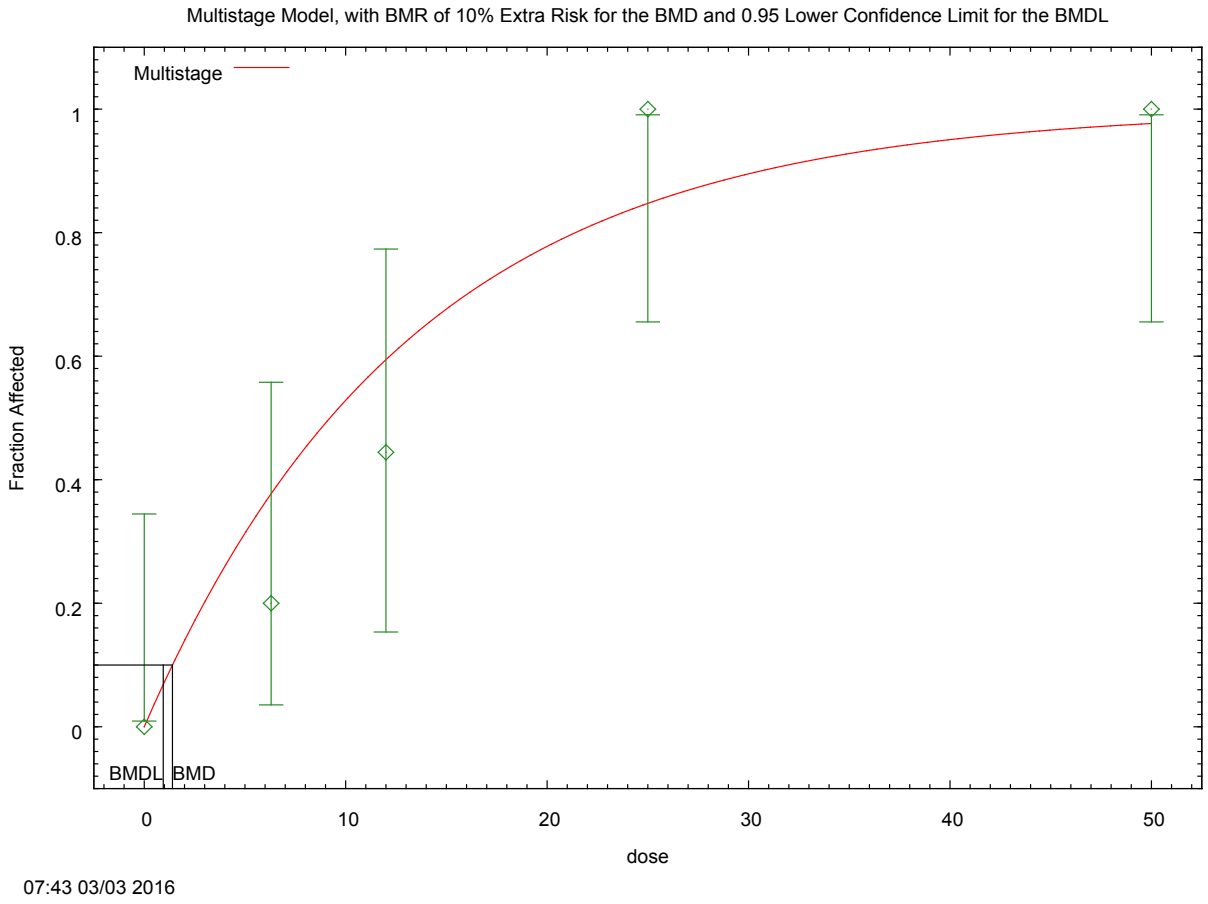
Table A-3. Model Predictions for the Incidence of Squamous Metaplasia of the Epiglottis in Male and Female Mice (Combined) Exposed to Antimony Trioxide (NTP 2016)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	3	1.04	0.79	0.00	0.48	-0.71	27.68	5.49	2.39
Logistic	3	0.85	0.84	-0.43	0.62	0.62	27.48	5.83	3.53
LogLogistic[d]	3	1.77	0.62	0.00	0.66	-0.86	28.64	5.79	3.17
LogProbit[d]	3	1.55	0.67	0.00	0.56	-0.89	28.31	5.73	3.25
Multistage (1-degree)[e,f]	***4***	***4.22***	***0.38***	***0.00***	***-1.16***	***-1.16***	***30.45***	***1.40***	***0.94***
Multistage (2-degree)[e]	4	0.70	0.95	0.00	0.05	0.59	25.41	4.41	1.74
Multistage (3-degree)[e]	3	0.27	0.97	0.00	0.24	-0.36	26.73	4.34	1.60
Multistage (4-degree)[e]	3	0.06	1.00	0.00	0.12	0.15	26.46	3.56	1.49
Probit	3	0.59	0.90	-0.34	0.51	0.51	27.12	5.48	3.28
Weibull[c]	3	0.61	0.89	0.00	0.48	-0.51	27.08	5.33	2.40

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Multistage 1 degree).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-2. Fit of 1-Degree Multistage Model to Data on Incidence of Epiglottal Squamous Metaplasia in Male and Female Mice Exposed to Antimony Trioxide (mg Sb/m^3)



A summary of the potential PODs (BMCLs for the selected models, LOAELs, or NOAELs for models without adequate fit) is presented in Table A-4.

Table A-4. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs) for Acute-Duration Inhalation MRL for Antimony

End point (reference)	PODs (mg Sb/m^3)	RDDR values[a]	HECs[b] (mg Sb/m^3)
Squamous metaplasia of the epiglottis in male and female rats (NTP 2016)	2.95 ($BMCL_{10}$)	0.162[c]	0.085
Chronic lung inflammation (NTP 2016)	12 (NOAEL)	0.545[c]	1.1
Squamous metaplasia of the epiglottis in male and female mice (NTP 2016)	0.94 ($BMCL_{10}$)	0.206[c]	0.035
Lung inflammation in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	0.203[d]	1.2
Degenerative changes in heart and altered EKG readings in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	1.060[d]	6.2

[a]RDDR values specific for each region of the respiratory tract (extrathoracic and pulmonary) were calculated using EPA's RDDR calculator with the average of the male and female terminal body weights of 0.189 and 0.0281 kg for rats and mice, respectively, and 4.0 kg for rabbits.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days for the NTP [2016] study and POD x 7 hours/24 hours x 5 days/7 days for the Brieger et al. [1954] study) by the RDDR value.
[c]Calculated using a particle size of 1.4 µm (sigma g of 1.9).
[d]Calculated using a particle size of 2 µm (sigma g of 1.9); this is an assumed value; the investigators noted that most of the particles were <2 µm, but did not provide any additional information.

BMCL = 95% lower confidence limit on the benchmark concentration; EKG = electrocardiogram; EPA = Environmental Protection Agency; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; RDDR = regional deposited dose ratio

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: HECs were calculated for each potential POD by adjusting for intermittent exposure (6 hours/24 hours, 5 days/7 days for NTP [2016] and 7 hours/day for Brieger et al. [1954]) and multiplying the POD_{ADJ} by the RDDR for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with the calculated average male and female terminal body weights of 0.189 and 0.0281 kg for rats and mice, respectively, for the NTP (2016) study and a reference body weight of 4.0 kg for the rabbits. The POD_{HEC} values are presented in Table A-4.

Was a conversion used from intermittent to continuous exposure? Yes, see previous section.

Other additional studies or pertinent information that lend support to this MRL: No human studies have evaluated the acute inhalation toxicity of antimony. In laboratory animals, the acute toxicity has been evaluated for stibine, antimony trisulfide, and antimony trioxide. These studies clearly identify the respiratory tract as one of the most sensitive targets of antimony toxicity (Brieger et al. 1954; NTP 2016; Price et al. 1979). A 30-minute exposure to 1.395 mg Sb/m^3 as stibine resulted in pulmonary edema and congestion and death in rats and guinea pigs (Price et al. 1979). Chronic lung inflammation was observed

in rabbits exposed to 19.9 mg Sb/m^3as antimony trisulfide for 5 days (7 hours/day) and in rats exposed to 25 mg Sb/m^3 as antimony trioxide for 12 exposures over a 16-day period (6 hours/day) (NTP 2016). NTP (2016) also found squamous metaplasia in the epiglottis of rats and mice exposed to 25 or 12 mg Sb/m^3, respectively. The primary extrarespiratory effects also observed following acute exposure were degenerative changes in the heart and altered EKG readings in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide.

There are limited data for comparing the relative toxicity of antimony compounds following acute inhalation exposure. The respiratory tract was a sensitive target in animals exposed to stibine, antimony trioxide, or antimony trisulfide, but differences in the study designs do not allow for a direct comparison. Additionally, there are no data to allow for an assessment of the influence of valence state on the respiratory toxicity of antimony.

Agency Contact (Chemical Manager): Melanie Buser

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Antimony
CAS Numbers: 7440-36-0
Date: April 2017
Profile Status: Draft for Public Comment
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 18
Species: Rats

Minimal Risk Level: 0.0003 [ ] mg/kg/day [X] mg Sb/m^3

Reference: Newton PE, Bolte HF, Daly IW, et al. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol 22(4):561-576.

Experimental design: Groups of 65 male and 65 female Fischer 344 rats were exposed to 0, 0.06, 0.51, or 4.50 mg/m^3 antimony trioxide dust (0, 0.05, 0.43, or 3.8 mg Sb/m^3, respectively) 6 hours/day, 5 days/week for 12 months followed by a 12-month observation period. Groups of five rats/sex were terminated after 6 and 12 months of exposure and at 6 months postexposure; the remaining animals were terminated 12 months postexposure. The MMAD was 3.76±0.84 µm with a geometric standard deviation of 1.79±0.326. The following parameters were used to assess toxicity: weekly detailed observations, body weight measurements (weekly for the first 13 weeks and monthly thereafter), ophthalmoscopic examination, hematological (hemoglobin, hematocrit, erythrocyte count, mean corpuscular hemoglobin, hemoglobin concentration, and volume, and total leukocyte counts) and clinical chemistry (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, fasting glucose, total protein, chloride, sodium, and potassium) indices assessed at 12, 18, and 24 months, and histopathological examination of the heart, nasal turbinates, larynx, trachea, lung, and peribronchial lymph nodes.

Effect noted in study and corresponding doses: No increases in mortality were observed. Corneal effects were observed during the study; however, the investigators noted that the effects were equally distributed among exposed and control groups and were similar to spontaneous degenerative conditions observed in Fischer 344 rats. The investigators noted a concentration-related increase in the occurrence of chromodacryorrhea (incidence data not provided); they noted that microscopic periodontal disease was also observed in some rats and that the chromodacryorrhea may be secondary to this effect. At the end of the recovery period, an increase in the occurrence of cataracts (focal posterior cataract, posterior subcapsular cataract, complete cataract) was observed (incidences of 6/55, 12/49, 18/64, and 19/60 were reported in Bio/Dynamics 1990); the incidence was statistically significant at ≥0.43 mg Sb/m^3 (Fisher Exact Test conducted by SRC). No treatment-related alterations in body weight gain, hematological indices, clinical chemistry indices, or lung weights were observed. At the end of the exposure period and at the end of the recovery period, statistically significant (Fisher Exact Test conducted by SRC) increases in the incidence of alveolar/intraalveolar macrophages were observed at ≥0.05 mg Sb/m^3. Histological alterations were observed in the lungs of rats killed at the end of the recovery periods: chronic interstitial inflammation at 0.43 (females only) and 3.8 mg Sb/m^3 and interstitial fibrosis at 3.8 mg Sb/m^3. Although a high incidence of lung inflammation was also observed in controls, the investigators noted that the inflammation observed in the controls was considered a "spontaneous lesion" and that the incidence and severity of the inflammation was concentration-related (see Table A-5). Increases in antimony trioxide lung clearance half-times were observed; the half-times (data reported in Bio/Dynamics 1990) in the male and female rats were 3.0 and 4.2 months, respectively, at 0.43 mg Sb/m^3 and 8.7 and 10.2 months,

respectively, at 3.8 mg Sb/m^3, as compared to 2.5 and 2.2 months, respectively, in the 0.05 mg Sb/m^3 group. No significant increases in the incidence of neoplastic lesions were observed.

Table A-5. Incidence and Severity of Chronic Interstitial Lung Inflammation in Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery (Newton et al. 1994)

	Concentration (mg Sb/m^3)			
Severity	0	0.05	0.43	3.8
Males				
Minimal	4/52 (12.5)[a]	7/52 (18.9)	12/53 (33.3)	0/52 (0)
Slight	19/52 (59.4)	27/52 (73)	24/53 (66.7)	14/52 (29.2)
Moderate	8/52 (25)	3/52 (8.1)	0/53 (0)	32/52 (66.7)
Moderately severe	1/52 (3.1)	0/52 (0)	0/53 (0)	2/52 (3.8)
Females				
Minimal	3/49 (9.1)	12/52 (30)	14/54 (29.1)	1/50 (2.1)
Slight	24/49 (72.7)	23/52 (57.5)	23/54 (47.9)	29/50 (60.4)
Moderate	6/49 (18.2)	5/52 (12.5)	11/54 (22.9)	18/50 (37.5)
Moderately severe	0/49 (0)	0/52 (0)	0/54 (0)	0/50 (0)

[a]Percentage of total lesions with a specific severity score.

Dose and end point used for MRL derivation: $BMCL_{10}$ of 0.10 mg Sb/m^3 ($BMCL_{HEC}$ of 0.008 mg Sb/m^3) for lung inflammation in female rats.

[ ] NOAEL [ ] LOAEL [X] $BMCL_{10}$

Four studies identified LOAEL values of <5 mg Sb/m^3 for lung effects in rats (Newton et al. 1994; NTP 2016; Watt 1983) and mice (NTP 2016). Watt (1983) found increases in the incidence of focal fibrosis, adenomatous hyperplasia, cholesterol clefts, and pneumocyte hyperplasia in rats exposed to 1.6 mg Sb/m^3 for 55 weeks. In rats and mice exposed to 2.5 mg Sb/m^3 as antimony trioxide for 2 years, inflammation, proteinosis, alveolar/bronchiolar hyperplasia, and fibrosis were observed in the lungs (NTP 2016). An increase in lung clearance times was observed in rats exposed to 3.8 mg Sb/m^3 as antimony trioxide for 12 months and an increase in the severity and incidence of chronic lung inflammation was observed at 0.43 (females only) and 3.8 mg Sb/m^3 was after a 1-year recovery period (Newton et al. 1994). Some non-respiratory effects have also been seen at similar concentrations, including lenticular degeneration in rats exposed to 0.43 mg Sb/m^3 (Newton et al. 1994), bone marrow hyperplasia in mice exposed to 2.5 mg Sb/m^3 (NTP 2016), and lymphoid hyperplasia in bronchial and/or mediastinal lymph nodes in rats and mice exposed to 2.5 mg Sb/m^3 (NTP 2016). Newton et al. (1994) identified the lowest LOAEL value for chronic interstitial lung inflammation and lenticular degeneration in rats exposed to 0.43 mg Sb/m^3 for 1 year with a 1-year recovery period; these effects were not observed at 0.05 mg Sb/m^3. The other chronic-duration studies identified higher LOAEL values.

BMD modeling was utilized to estimate the potential PODs for the histological alterations observed in lungs and eyes. The incidence data from the Newton et al. (1994) (Table A-6) studies were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined

BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. The results of the BMD modeling for lung inflammation in female rats is presented in Table A-7 and the model fit is presented in Figure A-5. The incidence data for lung inflammation in males were not considered suitable for modeling since only the highest concentration group showed a response; thus, the data provide limited information on the shape of the concentration-response curve. For lenticular degeneration, none of the available models provided an adequate fit to the data.

Table A-6. Incidence of Nonneoplastic Lesions in Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery (Newton et al. 1994)

	Concentration (mg Sb/m^3)			
Effect	0	0.05	0.43	3.8
Chronic lung inflammation in males	32/52	37/52	36/53	48/52[a]
Chronic lung inflammation in females	33/49	40/52	48/54[a]	48/50[a]
Lenticular degeneration	6/55	12/49	18/64[a]	19/60[a]

[a]Significantly different from controls.

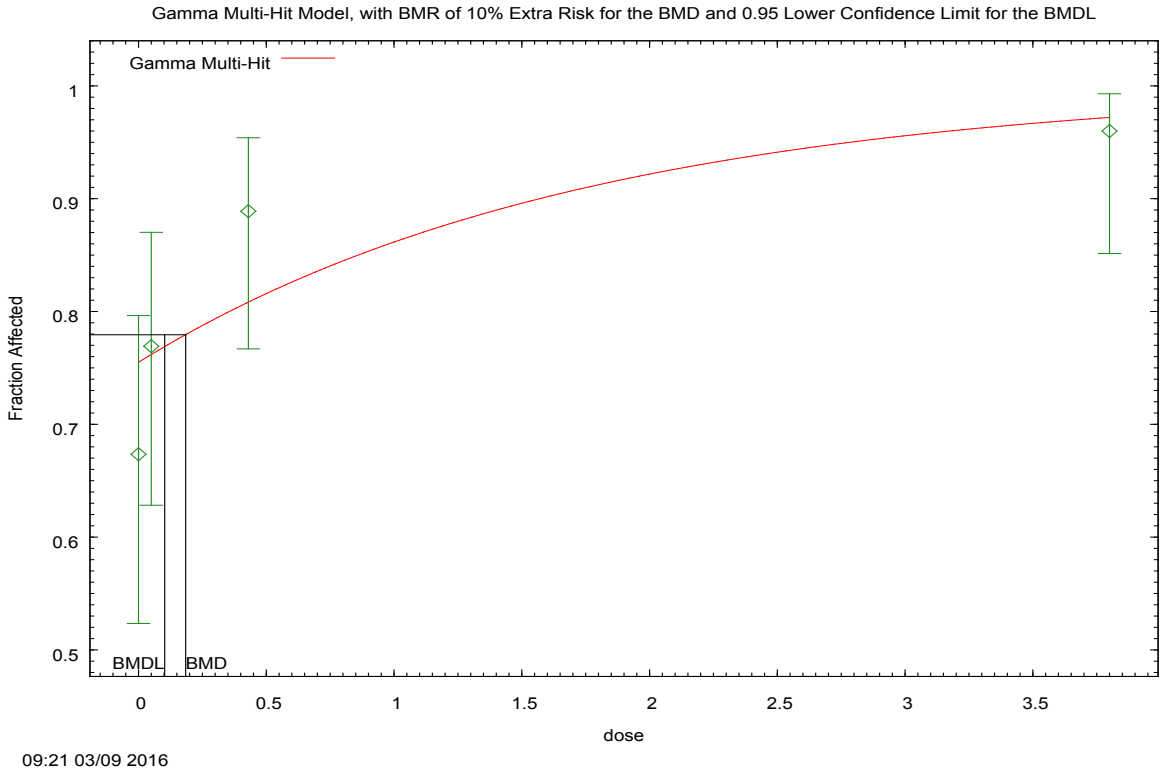
Table A-7. Model Predictions for Antimony Trioxide, Incidence of Chronic Lung Inflammation in Female Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery Period (Newton et al. 1994)

Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c,d]	***2***	***4.3***	***0.12***	***0.13***	***1.51***	***1.51***	***181.03***	***0.18***	***0.10***
Logistic	2	4.63	0.10	0.07	1.56	1.56	181.38	0.22	0.13
LogLogistic[e,f]	2	1.15	0.56	-0.43	0.44	-0.81	177.59	0.04	0.01
LogProbit[d]	2	5.21	0.07	0.26	1.47	1.47	181.64	ND	ND
Multistage (1-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Multistage (2-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Multistage (3-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Probit	2	4.9	0.09	0.03	1.62	1.62	181.68	ND	ND
Weibull[c]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. BMCLs for models providing adequate fit were sufficiently close; therefore the model with the lowest AIC was selected
[e]Slope restricted to ≥1.
[f]Model considered an outlier because the BMCL was 10 times lower than the other models.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-5. Fit of Gamma Model to Data on Incidence of Lung Interstitial Inflammation in Female Rats Exposed to Antimony Trioxide (mg Sb/m^3)



The PODs for each end point are presented in Table A-8; for lung inflammation in males and lenticular degeneration, the NOAEL was used as the POD since the incidence data were not considered suitable for BMD modeling. The lowest POD_{HEC} was 0.008 mg Sb/m^3 for lung inflammation in female rats.

Table A-8. Summary of Potential Points of Departure (PODs) for Derivation of Chronic-Duration Inhalation MRL for Antimony

End point (reference)	POD (mg Sb/m^3)	RDDR[a]	HEC[b] (mg Sb/m^3)
Chronic interstitial inflammation in male rats (Newton et al. 1994)	0.43 (NOAEL)	0.330	0.025
Chronic interstitial inflammation in female rats (Newton et al. 1994)	0.10 ($BMCL_{10}$)	0.436	0.008
Lenticular degeneration in rats (Newton et al. 1994)	0.05 (NOAEL)	2.797	0.025

[a]RDDR values specific for each region of the respiratory tract (pulmonary and extrarespiratory) were calculated using EPA's RDDR calculator with reference body weights of 0.380 and 0.229 kg for male and female rats in the Newton et al. (1994) study and particle size of 3.76 µm (sigma g of 1.79).
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days) by the RDDR value.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure; RDDR = regional deposited dose ratio

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustments
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Not applicable.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: HECs were calculated for each potential POD by adjusting for intermittent exposure (6 hours/24 hours, 5 days/7 days) and multiplying the POD_{ADJ} by the RDDR for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with reference body weights of 0.380 and 0.229 kg for male and female rats and particle size of 3.76 µm (sigma g of 1.79). The POD_{HEC} values are presented in Table A-8.

Was a conversion used from intermittent to continuous exposure? Yes, see previous section.

Other additional studies or pertinent information that lend support to this MRL: The toxicity of airborne antimony has not been extensively studied in humans. Several occupational exposure studies have reported lung effects (pneumoconiosis, chronic bronchitis) in workers at antimony smelters (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Schnorr et al. 1995). Signs of upper respiratory tract irritation including bleeding of the nose, rhinitis, upper airway inflammation, and laryngitis (Potkonjak and Pavlovich 1983; Renes 1953) have also been reported in workers. Other effects that have been observed in workers include altered EKGs (Brieger et al. 1954) and dermatitis, which is likely due to direct contact with skin (Potkonjak and Pavlovich 1983; Renes 1953). One study also reported reproductive disturbances and developmental effects (decreases in infant growth) in female workers exposed to metallic antimony, antimony trioxide, and antimony pentasulfide (Belyaeva 1967). Although some studies provided exposure levels, these studies were not considered suitable for derivation of chronic MRLs because many studies did not include control groups, wide ranges of antimony levels were reported, and many involved co-exposure to other compounds including arsenic.

A number of studies have evaluated the chronic toxicity of antimony compounds in rats and mice. These studies provide strong evidence that the respiratory tract is the primary target of antimony toxicity, which is supported by the systematic review of the toxicity data that concluded that respiratory tract toxicity is a presumed health effect in humans. The lowest LOAEL values were identified in three studies involving antimony trioxide exposure for 1–2 years (Newton et al. 1994; NTP 2016; Watt 1983). Higher LOAELs for lung effects were identified for other antimony compounds: 17.5 mg Sb/m^3 as antimony ore for interstitial fibrosis (Groth et al. 1986) and 84 mg Sb/m^3 as antimony trisulfide for lipoid pneumonia (Gross et al. 1952). Although these LOAELs are higher than those identified for antimony trioxide, the available data do not allow a comparison between compounds since adverse effects were often observed at the lowest concentration tested. A summary of the NOAEL and LOAEL values for the respiratory effects is presented in Table A-9. In addition to the pulmonary effects, effects have also been observed in the lymph nodes (lymphoid hyperplasia in bronchial and mediastinal lymph nodes), eyes (lenticular degeneration), and bone marrow (hyperplasia); the LOAELs for these effects (see Table A-9) are similar to those identified for respiratory effects.

There are limited data to compare the relative toxicity of antimony compounds. Chronic studies have tested antimony trioxide, antimony trisulfide, and antimony ore; the respiratory tract was the most sensitive target in all of these studies. It is difficult to compare the potency of the different compounds because in most cases, the lowest concentration tested was a LOAEL. No data were available to compare the toxicity of trivalent and pentavalent antimony compounds.

Table A-9. Summary of NOAEL and LOAEL Values for Effects Observed in Target Tissues

Effect	NOAEL (mg Sb/m^3)	LOAEL (mg Sb/m^3)	Reference
Chronic interstitial inflammation in female rats exposed to antimony trioxide for 1 year	0.05	4.3	Newton et al. 1994
Chronic interstitial inflammation in male rats exposed to antimony trioxide for 1 year	0.43	3.8	Newton et al. 1994
Lenticular degeneration in rats exposed to antimony trioxide for 1 year	0.05	0.43	Newton et al. 1994
Lipoid pneumonia in rats exposed to antimony trisulfide for 14.5 months		84	Gross et al. 1952
Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony trioxide for 1 year		36	Groth et al. 1986
Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony ore for 1 year		17.5	Groth et al. 1986
Focal fibrosis, pneumocyte hyperplasia in rats exposed to antimony trioxide for 55 weeks		1.6	Watt 1983
Lung inflammation, proteinosis, alveolar epithelial hyperplasia, bronchiole epithelial hyperplasia, lung fibrosis in rats exposed to antimony trioxide for 2 years		2.5	NTP 2016
Nasal respiratory epithelial hyperplasia in rats exposed to antimony trioxide for 2 years		2.5	NTP 2016
Lymphoid hyperplasia in bronchial and mediastinal lymph nodes in rats exposed to antimony trioxide for 2 years		2.5	NTP 2016
Lung inflammation, alveolar fibrosis, pleural fibrosis and inflammation, alveolar and bronchiolar epithelial hyperplasia in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016
Nasal respiratory epithelial inflammation in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016
Bone marrow hyperplasia in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016
Lymphoid hyperplasia of bronchial lymph nodes in mice exposed to antimony trioxide for 2 years		2.5	NTP 2016

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Agency Contact (Chemical Manager): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Antimony
CAS Numbers: 7440-36-0
Date: April 2017
Profile Status: Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 2
Species: Mice

Minimal Risk Level: 1 [X] mg Sb/kg/day [ ] ppm

Reference: NTP. 1992. Toxicology studies of antimony potassium tartrate in F344/N rats and B6C3F1/N mice (drinking water and intraperitoneal injection studies). National Toxicology Program, Research Triangle Park, NC. NTP TOX 11.

This study is also reported in: Dieter MP, Jameson CW, Elwell MR. 1991. Comparative toxicity and tissue distribution of antimony potassium tartrate in rats and mice dosed by drinking water or intraperitoneal injection. J Toxicol Environ Health 34:51-82.

Experimental design: Groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 0.30, 0.65, 1.25, 2.5, or 5.0 mg/mL antimony potassium tartrate (99–100% purity) in drinking water for 14 days. The investigators used water consumption data and body weight averages to calculate doses of 0, 59, 98, 174, 273, and 407 mg/kg/day antimony potassium tartrate (0, 21, 36, 63, 99, and 150 mg Sb/kg/day). The following parameters were evaluated to assess toxicity: twice daily observations, body weight measurements (days 1 and 8 and at termination), water consumption (days 7 or 8 and day 15), organ weights, histopathology of major tissues and organs in control and high-dose groups (five mice/sex/group) and all early deaths, and histopathological examination of the liver and forestomach of mice in all groups (five mice/sex/group).

Effect noted in study and corresponding doses: One female mouse in the 150 mg Sb/kg/day group died prior to the end of the study. On day 8, decreases in body weight gain were observed in males exposed to 99 mg Sb/kg/day and in males and females exposed to 150 mg Sb/kg/day. However, by the end of the study, the final weights of all antimony groups were within 93% of the controls. Decreases in water consumption were observed at all antimony levels. The investigators noted that overt signs of toxicity (rough haircoat, emaciation, abnormal posture, hypoactivity, and decreased fecal material, consistent with avoidance of the antimony potassium tartrate containing water) were observed, but did not specify if this was observed in all groups. Histological alterations were observed in the forestomach and liver of mice in the 150 mg/kg/day group. In the forestomach, focal areas of ulceration with necrosis and inflammation of the squamous mucosa were observed; the incidence was not reported, although the investigators noted that gross forestomach lesions were observed in one male and three females. In the liver, minimal to moderate cytoplasmic vacuolization was observed in all mice in the 150 mg Sb/kg/day group; the vacuolization had a centrilobular distribution with some extension into portal areas.

Dose and end point used for MRL derivation: The NOAEL of 99 mg Sb/kg/day for liver lesions was selected as the POD for the MRL.

[X] NOAEL [ ] LOAEL

BMD modeling was not conducted since lesions were only observed in the high-dose group. The transient decrease in body weight observed at 99 and 150 mg Sb/kg/day was not selected as the POD because this decrease may have been the result of decreased water consumption likely due to taste aversion.

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? The investigators calculated antimony potassium tartrate doses based on water consumption and body weight data.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Studies conducted in the 1920s and 1940s demonstrate that antimony potassium tartrate is a gastrointestinal irritant in humans (Dunn 1928) and animals (as reviewed by Elinder and Friberg 1986), resulting in vomiting and diarrhea shortly after exposure. Houpt et al. (1984) demonstrated that the mean latency to vomit was 30 minutes after dogs drank 4.8 mg Sb/kg as antimony potassium tartrate. These gastrointestinal effects are likely due to the antimony concentration rather than the dose. NTP (1992) evaluated the acute toxicity of antimony potassium tartrate in 14-day drinking water studies in rats and mice. In rats, the highest concentration (61 mg Sb/kg/day) did not result in significant alterations in body weight or histopathological alterations in major tissues and organs. In mice, exposure to 150 mg Sb/kg/day resulted in focal ulceration in the forestomach and minimal to moderate hepatocellular cytoplasmic vacuolization. Exposure to 99 and 150 mg Sb/kg/day resulted in a transient decrease in body weight gain; at termination, body weights were within 93% of controls. The decreases in body weight may have been secondary to the dramatic decrease in water intake, which was also observed in the exposed mice.

Support for identifying the liver as the critical effect for antimony is supported by intermediate-duration studies in which histological alterations were observed in rats exposed to antimony metal or antimony trioxide (Sunagawa 1981) and increases in alanine aminotransferase and aspartate aminotransferase in humans receiving injections of pentavalent antimony (Andersen et al. 2005). Insufficient evidence is available to allow for a comparison of the hepatotoxicity of different antimony compounds or valence states. The absorption rate of antimony potassium tartrate is greater than that of other antimony compounds (ICRP [1981] recommends rates of 10 and 1%, respectively), which likely results in a higher toxicity. More side effects (all effects) were observed in patients treated with antimony potassium tartrate than with pentavalent antimony compounds, although studies directly comparing the valency states on antimony hepatotoxicity were not identified. Alverez et al. (2005) reported greater cardiotoxicity and lethality in guinea pigs receiving intramuscular injections of 10 mg Sb/kg/day as antimony potassium tartrate, as compared to guinea pigs administered 16 mg Sb/kg/day as meglumine antimoniate.

Agency Contact (Chemical Manager): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Antimony
CAS Numbers: 7440-36-0
Date: April 2017
Profile Status: Draft for Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 10
Species: Rats

Minimal Risk Level: 0.0006 [X] mg Sb/kg/day [ ] ppm

Reference: Poon R, Chu I, Lecavalier P, et al. 1998. Effects of antimony on rats following 90-day exposure via drinking water. Food Chem Toxicol 36:21-35.

Experimental design: Groups of 15 male and 15 female Sprague-Dawley rats were exposed to 0, 0.5, 5, 50, or 500 ppm antimony as potassium antimony tartrate (99.95% pure) in drinking water for 13 weeks. Based on average water consumption and body weight data, the investigators calculated antimony doses of 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day in males and 0, 0.06, 0.64, 6.13, and 45.69 mg Sb/kg/day in females. An additional group of 10 male and 10 female rats was exposed to 0 or 500 ppm for 13 weeks followed by a 4-week recovery period. The following parameters were used to assess toxicity: weekly body weight, food consumption, and water intake measurements; hematological indices (erythrocyte counts hemoglobin, hematocrit, mean corpuscular volume, and total and differential leukocyte counts); clinical chemistry indices (albumin, alkaline phosphatase, aspartate aminotransferase, creatine kinase, sorbitol dehydrogenase, bilirubin, calcium, cholesterol, creatinine, glucose, inorganic phosphate, lactic dehydrogenase, total protein, urea nitrogen, and uric acid); serum thyroxin and thyroid hormone binding ratio; organ weights (brain, thymus, heart, kidney, spleen, liver); and histopathological examination (brain, pituitary, thyroid and trachea, salivary glands, thymus, lung, heart, liver, kidneys, adrenals, spleen, pancreas, esophagus, stomach, small and large intestine, urinary bladder, skin, bone marrow, and gonadal tissues).

Effect noted in study and corresponding doses: No alterations in survival or overt signs of toxicity were observed. Decreases in water consumption (35% lower than controls) and food consumption (12%) were observed in the 42.17/45.69 mg Sb/kg/day group during the exposure period but not during the recovery period.

- Body weight: A decrease in body weight gain, significant in males starting at week 6 and females at week 12, was observed at 42.17/45.69 mg Sb/kg/day; the body weights appeared to be within 10% of the controls. A significant increase in relative kidney weights was observed in the 42.17/45.69 mg Sb/kg/day group.
- Metabolic: A dose-related decrease (15–17%) in serum glucose levels was observed in females exposed to ≥0.64 mg Sb/kg/day; lower values were also observed in the males, but were not statistically different from controls. No differences in serum glucose levels were observed at the end of the recovery period. ATSDR notes that serum glucose levels in all groups (including controls) were higher than the range of normal values reported by the animal supplier (Charles River Laboratories 2006).
- Clinical chemistry: Decreases in serum creatinine levels and alkaline phosphatase levels were observed in males and females exposed to 42.17/45.69 mg Sb/kg/day at the end of the exposure period, but not at the end of the observation period. A decrease (24%) in serum cholesterol level

was observed in females exposed to 45.69 mg Sb/kg/day; the toxicological significance of this alteration is not known.

- Hematological: Decreases in red blood cells and platelet counts and increases in mean corpuscular volume were observed in males exposed to 42.17 mg Sb/kg/day; in females, the only hematological alteration was an increase in monocytes at 45.69 mg Sb/kg/day. Significant increases in hepatic ethoxyresorufin-O-deethylase and glutathione-S-transferase activities were observed in males at 42.17 mg Sb/kg/day; glutathione-S-transferase activity was also increased in females at 45.69 mg Sb/kg/day.
- Hepatic: Histological alterations included anisokaryosis in the liver in all antimony exposed groups; dose-related increases in the severity were also observed. Anisokaryosis was also observed at the end of the recovery period. Other hepatic effects included an increase in hepatocellular portal density in all antimony groups and minimal nuclear hyperchromicity at ≥0.56/0.64 mg Sb/kg/day, but there was not consistent dose-response relationship for this end point. The severity scores for the anisokaryosis were 0.1, 0.6, 1.0, 1.9, and 2.8 in the 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day males; a severity score of 1 is considered minimal, 2 is mild, and 3 is moderate. In the females, the respective severity scores were 0.9, 1.5, 2.3, 2.3, and 2.6. Similarly, the increase in portal density in the hepatocellular cytoplasm was graded as minimal at the two lowest doses in the males and females and mild at the two highest doses. The anisokaryosis, hepatocellular density, and hyperchromicity are considered adaptive changes and were not considered adverse.
- Skeletal: In the bone marrow, an increase in myeloid hyperplasia was observed at ≥5.58 mg Sb/kg/day in males and ≥0.64 mg Sb/kg/day in females.
- Spleen: The following alterations were observed in the spleen: sinus congestion at ≥0.56 mg Sb/kg/day in males, sinus hyperplasia at 42.17 mg Sb/kg/day in males and ≥0.64 mg Sb/kg/day in females, and arterial cuff atrophy at 42.17 mg Sb/kg/day in males. In the recovery period, increases in incidence of sinus congestion (males only), arterial cuff atrophy, periarteriolar lymphocyte sheath cell density, and sinus hematopoiesis were observed.
- Endocrine: Statistically significant increases in thyroid hormone binding ratio were observed in females at 6.13 and 45.69 mg Sb/kg/day. Thyroid histological alterations included an increase in epithelial height, reduced follicle size, and nuclear vesiculation in antimony rats; an increased occurrence of collapsed follicles was observed in the antimony recovery group. These thyroid effects did not show a strong dose-response relationship and did not appear to affect thyroid function; the investigators did not consider them adverse.

Dose and end point used for MRL derivation: NOAEL of 0.06 mg Sb/kg/day for decreased serum glucose in female rats.

[X] NOAEL [ ] LOAEL

Three studies identified LOAEL values of 0.1–0.64 mg Sb/kg/day in rats exposed to antimony trichloride or antimony potassium tartrate. The effects observed at these concentrations included altered vasomotor response in rat pups exposed to antimony trichloride during gestation and/or lactation and on PNDs 22–60 (Angrisani et al. 1988; Rossi et al. 1987), decreases in pup growth on PNDs 10–60 (Rossi et al. 1987), and decreases in serum glucose levels in rats exposed to antimony potassium tartrate for 13 weeks (Poon et al. 1998). These three end points were considered for the basis of the intermediate-duration MRL. Developmental toxicity and decreases in serum glucose levels were both considered suspected health effects in humans based on the systematic review of the available data on antimony; of the two developmental effects, only the decrease in growth was considered due to the uncertainty associated with estimating the dose for the vasopressor studies. In these studies, rats were exposed during gestation and/or lactation and then exposed on PNDs 22–60; the 0.1 mg Sb/kg/day dose is an estimate of the

postnatal exposure, but does not include an estimate of prenatal exposure or exposure via breastmilk. BMD modeling was considered for the decreases in serum glucose levels and decreases in pup body weight on PNDs 10 and 22. The serum glucose levels (Table A-10) and pup body weights (Table A-11) were fit to all available continuous models in EPA's BMDS (version 2.6.0). The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For all models, a BMR of 1 standard deviation change from the control was used.

Table A-10. Serum Glucose Concentrations in Female Rats Exposed to Antimony Potassium Tartrate for 13 Weeks (Poon et al. 1998)

Dose (mg Sb/kg/day)	Serum glucose concentration (mean ± standard deviation, mg/dL)
0	242±55
0.06	217±22
0.64	200±25[a]
6.13	207±27[a]
45.69	198±25[a]

[a]Significantly different from controls

Table A-11. Alterations in Pup Body Weight on Postnatal Days (PNDs) 10 and 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation (Rossi et al. 1987)

	Pup body weight (mean ± standard error)	
Dose (mg Sb/kg/day)	PND 10	PND 22
0	23±1.8 (73)[a]	58±5.1 (66)
0.07	20±2.6 (80)	52±4.0 (72)
0.7	17±0.4[b] (63)	31±2.8[b] (56)

[a]Number in parentheses is the number of pups examined; data were not presented in a way that would allow analysis on a per-litter basis
[b]Significantly different from controls

None of the models provided adequate fit to the serum glucose data or the PND 10 body weight data. Although adequate statistical fit was found for the PND 22 body weight data (model results are presented in Table A-12), the BMDL for the model with the lowest AIC (Exponential, model 3) was 0.72 mg Sb/kg/day, which is the same value as the empirical LOAEL identified in the study and was not considered a suitable basis for an MRL. Thus, a NOAEL/LOAEL approach was utilized to identify the POD for the intermediate-duration oral MRL. The NOAEL and LOAEL values for the decreased serum glucose level and the decreased pup body weight were similar and the end point with the lowest LOAEL (decreased serum glucose level) was selected as the basis of the MRL.

Table A-12. Model Predictions for Antimony, Alterations in Pup Body Weight on Postnatal Day (PND) 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation (Rossi et al. 1987)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Linear[e]	<0.0001	<0.0001	0.54	0.05	NA	-0.44	1,562.44	NA	NA
Nonconstant variance									
Exponential (model 2)[d]	<0.0001	0.61	0.27	0.03	NA	-0.31	1,540.28	1.32	0.86
Exponential (model 3)[d,e]	***<0.0001***	***0.61***	***0.27***	***0.03***	***NA***	***-0.31***	***1,540.28***	***1.32***	***0.72***
Exponential (model 4)[d]									ND
Exponential (model 5)[d]									ND
Hill[d]									ND
Linear[f]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.81
Polynomial (2-degree)[f]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.80
Power[d]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.71

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model did not provide adequate fit to the variance data. With nonconstant variance model applied, all models (except for the Exponential 4, and 5, and Hill models) provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Exponential 3; the Exponential 2 and 3 had the same AIC, so the model with the more conservative BMDL was selected out of these two).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable; ND = not determined (BMDL computation failed); SD = standard deviation

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Investigators calculated antimony potassium tartrate doses based on water consumption and body weight data.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: Several studies have evaluated the intermediate-duration toxicity of antimony compounds. Observed effects include reductions in body weight gain, hematological effects (alterations in red blood cell and platelet levels), decreases in serum glucose levels, thyroid (epithelial alterations), and developmental effects (decreased pup body weight and altered vasomotor response in pups). The results of several 12–24-week studies provide evidence for compound-specific differences in toxicity that are likely reflective of differences in the relative absorption of the compounds. More soluble compounds such as antimony potassium tartrate and antimony trichloride appear to be more toxic than antimony trioxide; see Table A-13 for a list of LOAELs for different antimony compounds.

Based on the limited available data, the toxicity of antimony potassium tartrate appears to be higher than antimony metal and antimony trioxide, which is likely due to the differences in absorption. ICRP (1981) recommends an absorption rate of 10% for antimony potassium tartrate and 1% for all other antimony compounds. A study (Alkhawajah et al. 1996) comparing the developmental toxicity of antimony trichloride (trivalent), sodium stibogluconate (pentavalent), and meglumine antimonate (pentavalent) in rats following intramuscular injections reported similar effects for the three compounds; although no direct comparisons were made, the magnitude of the alterations (decreases in fetal viability and body weight) appears to be similar for the three compounds.

Table A-13. List of NOAEL and LOAEL Values in Rats Exposed to Antimony or Antimony Compounds for Intermediate Durations

Effect, duration (reference)	Compound	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)
Altered vasomotor response in pups exposed during lactation (maternal dose was 0.8 mg Sb/kg/day) and post-lactation on PNDs 22–60 (Angrisani et al. 1988)	Antimony trichloride in drinking water		0.1 (post-weaning dose)
Altered vasomotor response in pups exposed during gestation and lactation (maternal dose was 0.7 mg Sb/kg/day) and post-lactation on PNDs 22–60 (Rossi et al. 1987)	Antimony trichloride in drinking water		0.1 (post-weaning dose)
Decreased pup growth on PNDs 10–60 in pups exposed during gestation, lactation, and postnatally (Rossi et al. 1987)	Antimony trichloride in drinking water	0.07	0.7
Decreases in serum glucose in female rats exposed for 13 weeks (Poon et al. 1998)	Antimony potassium tartrate in drinking water	0.06	0.64
Decreased red blood cell count in male rats exposed for 24 weeks (Sunagawa 1981)	Antimony metal in diet		620
Cloudy swelling in hepatic cords in male rats exposed for 24 weeks (Sunagawa 1981)	Antimony metal in diet		620
Increased disorder of hepatic cords in male rats exposed for 24 weeks (Sunagawa 1981)	Antimony trioxide in diet	370	740
No alterations in hematological, serum clinical chemistry, or histopathology of major tissues and organs in rats exposed for 13 weeks (Hext et al. 1999)	Antimony trioxide in diet	1,408	

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Agency Contact (Chemical Manager): Melanie Buser

APPENDIX B. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ANTIMONY

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to antimony, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to antimony:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

B.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to antimony. The inclusion criteria used to identify relevant studies examining the health effects of antimony are presented in Table B-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

B.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of antimony. Studies for other sections of the toxicological profile were also identified in the literature search and screen step. Although these studies were not included in the systematic review process, the results of some studies (e.g., parenteral administration, mechanistic studies, toxicokinetic studies) were considered in the final steps of the systematic review. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of antimony have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest.

APPENDIX B

Table B-1. Inclusion Criteria for the Literature Search and Screen

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Endocrine effects
Dermal effects
Ocular effects
Body weight effects
Metabolic effects
Other systemic effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Cancer

B.2.1 Literature Search

The following databases were searched in February 2015; the literature search was intended to update the existing toxicological profile for antimony (ATSDR 1992), and thus, the literature search was restricted to studies published between January 1990 to February 2015:

- PubMed
- National Library of Medicine's TOXLINE
- Scientist and Technical Information Network's TOXCENTER
- National Pesticide Information Retrieval System (NPIRS)
- Toxic Substances Control Act Test Submissions (TSCATS) and TSCATS2

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

The search strategy used the chemical name, CAS numbers (i.e., 7440-36-0, 1315-04-4, 1314-60-9, 28300-74-5, 10025-91-9, 1309-64-4, 1345-04-6, 7803-52-3) synonyms, and Medical Subject Headings (MeSH) terms for antimony. A total of 5,489 records were identified and imported into EndNote (version 5). After the identification and removal of 546 duplicates by EndNote, the remaining 4,943 records were moved to the literature screening step.

B.2.2 Literature Screening

A two-step process was used to screen the literature search results to identify relevant studies examining the health effects of antimony:

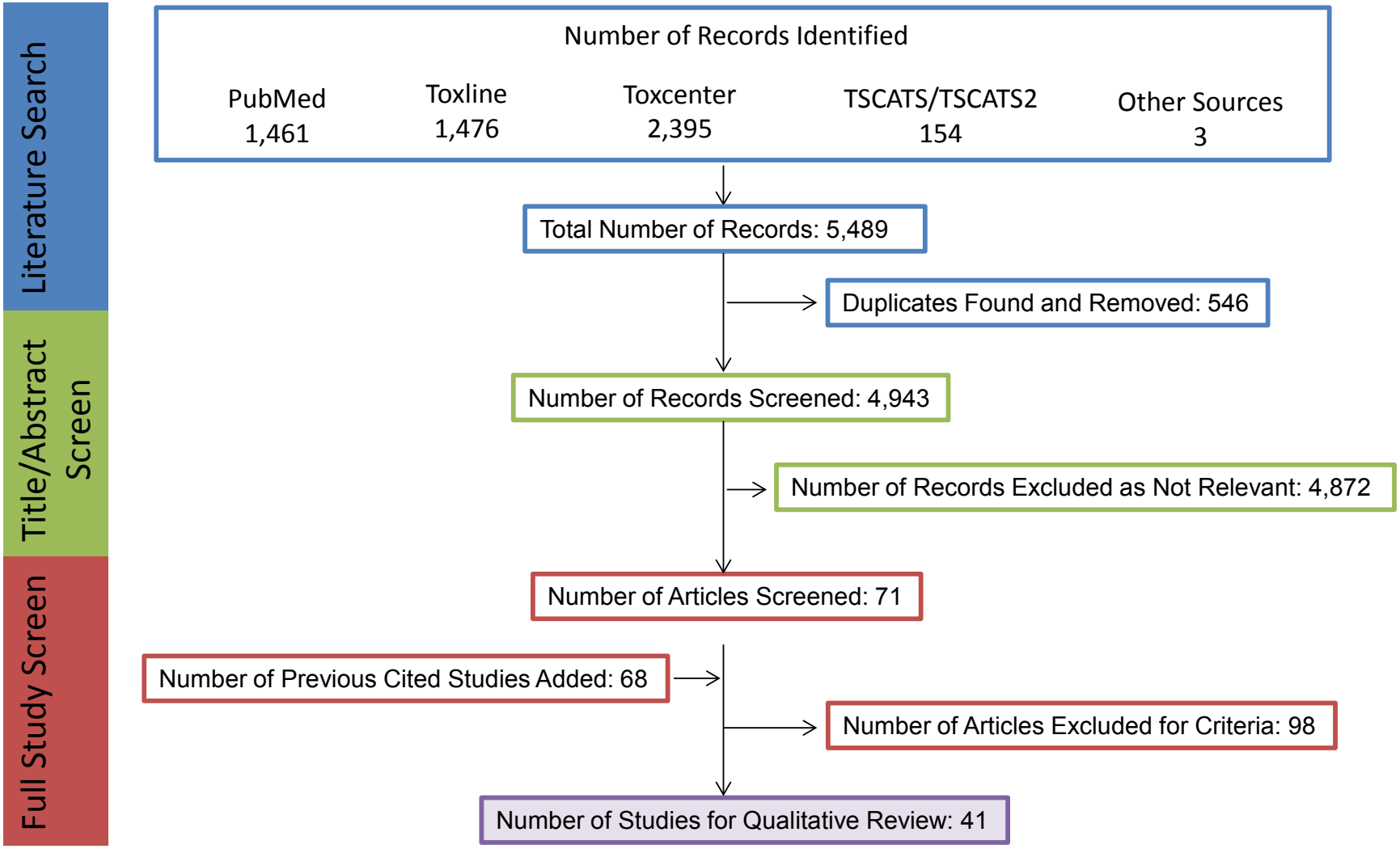
- Title and Abstract Screen
- Full Text Screen

Title and Abstract Screen. Within the Endnote library, titles and abstracts were screened manually for relevance. Studies that were considered relevant were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study did not meet the inclusion criteria (Table B-1). In the Title and Abstract Screen step, 4,946 records were reviewed; 71 studies were considered relevant to Section 3.2 of the toxicological profile and were moved to the next step in the process.

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the Title and Abstract Screen step. Each study was reviewed to determine whether it met the inclusion criteria; however, the quality of the studies was not evaluated at this step of the process. In addition to these 71 studies identified in the update literature search, 68 studies cited in the supplemental document for the existing profile were included in the full study screen, bringing the total number of studies for the qualitative review to 139. Of the 139 studies undergoing Full Text Screen, 98 studies did not meet the inclusion criteria; some of the excluded studies were used as background information on toxicokinetics or mechanisms of action or were relevant to other sections of the toxicological profile.

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. Literature Search and Screen for Antimony Health Effect Studies



B.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms in Distiller. A summary of the type of data extracted from each study is presented in Table B-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

A summary of the extracted data for each study is presented in the Supplemental Document for Antimony and overviews of the results of the inhalation, oral, dermal exposure studies are presented in Section 3.2 of the profile and in the Levels Significant Exposures tables in Section 3.2 of the profile (Tables 3-1, 3-3, and 3-5, respectively).

B.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for antimony identified in human and animal studies are presented in Tables B-3 and B-4, respectively. The available human studies examined a limited number of end points and reported respiratory, cardiovascular, gastrointestinal, musculoskeletal, immunological, reproductive, and developmental effects. Animal studies examined a number of end points following inhalation, oral, or dermal exposure. These studies examined most systemic end points and reported respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, and metabolic effects. Additionally, animal studies have reported immunological, reproductive, and developmental effects.

Respiratory, cardiovascular (damage to the myocardium and/or EKG alterations), gastrointestinal, metabolic (alterations in blood glucose levels), and developmental effects were considered sensitive outcomes, i.e., effects were observed at low concentrations or doses. Studies examining these potential outcomes were carried through to Step 4 of the systematic review.

Table B-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

Table B-3. Overview of the Health Outcomes for Antimony Evaluated In Human Studies

	Systemic effects																	
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Metabolic	Other	Immunological effects	Neurological effects	Reproductive effects	Developmental effects	Cancer
Inhalation studies																		
Observational	7	2(1)	3											1	2	1	1	2
	5	2	3											1	1	1	1	1
Experimental																		
Oral studies																		
Observational	1	3(0)			1	1		1					1		1		2[a]	2
	0	2			1	0		0					0		0		1	1
Experimental																		
Dermal studies																		
Observational									3	1								
									3	1								
Experimental																		

Number of studies examining end point	0	1	2	3	4	5–9	≥10		
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10		

Numbers in parentheses represent those studies looking at the specific cardiovascular end points of interest to this systematic review (damage to the myocardium and/or EKG alterations).

[a]One study (Zheng et al. 2014) was excluded because it measured risk of "adverse pregnancy outcome" but did not provide information on the end points examined and was not considered suitable for the systematic review.

Table B-4. Overview of the Health Outcomes for Antimony Evaluated in Experimental Animal Studies

	Systemic effects																	
	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Endocrine	Dermal	Ocular	Body weight	Metabolic	Other	Immunological effects	Neurological effects	Reproductive effects	Developmental effects	Cancer
Inhalation studies																		
Acute-duration	5	2(1)				2	3	1			3							
	5	1				1	2	0			0							
Intermediate-duration	4	6		4		2	2	1			5					1	1	
	4	3		0		1	1	1			0					1	1	
Chronic-duration	8	7	6	1	3	6	6	6		2	7		4	7	3	6		7
	6	2	1	0	2	0	1	0		2	2		0	4	0	1		5
Oral studies																		
Acute-duration	2	2	3		2	2	2	2			3							
	0	0	2		0	1	0	0			1							
Intermediate-duration	2	4(2)	2	7	1	4	3	2	1	1	11	1	1	1		4	3	
	0	1	0	4	0	2	0	0	0	0	5	1	1	1		0	3	
Chronic-duration		1(0)				1					2	1						2
		0				0					0	1						0
Dermal studies																		
Acute-duration									2	6				1				
									1	2				1				
Intermediate-duration		1				1	1		1	1	1					1		
		0				0	0		0	1	0					0		
Chronic-duration									4	4								
									1	1								

Number of studies examining end point	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

Numbers in parentheses represent those studies looking at the specific cardiovascular end points of interest to this systematic review (damage to the myocardium and/or EKG alterations).

B.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

B.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables B-5, B-6, and B-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table B-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table B-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table B-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?
Other bias
Did the study design or analysis account for important confounding and modifying variables?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of antimony health effects studies (observational epidemiology and animal experimental studies) are presented in Tables B-8 and B-9, respectively.

Table B-8. Summary of Risk of Bias Assessment for Antimony—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects							
Cohort studies							
Jones 1994 (antimony metal and antimony trioxide)	–	–	+	NA	–	+	Second
Renes 1953 (antimony oxides)	NA	–	+	+	+	+	Second
Schnorr et al. 1995 (antimony oxides)	+	–	+	–	+	+	Second
Cross-sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	–	+	+	+	+	Second
Cooper et al. 1968 (antimony trioxide)	NA	–	+	NA	+	+	Second
Case series							
Potkonjak and Pavlovich 1983 (antimony oxides)	NA	–	+	NA	+	+	Second
Taylor 1966 (antimony trichloride)	NA	–	+	–	–	+	Third
Outcome: Cardiovascular effects (myocardium damage and/or EKG alterations)							
Cross Sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	-	+	+	+	+	Second

Table B-8. Summary of Risk of Bias Assessment for Antimony—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Gastrointestinal Effects							
Cohort studies							
Renes 1953 (antimony oxides)	NA	–	+	+	+	+	Second
Cross-sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	–	+	+	+	+	Second
Case series							
Taylor 1966 (antimony trichloride)	NA	–	+	–	–	+	Third
Outcome: Developmental Effects							
Cohort studies							
Belyaeva 1967 (antimony metal, antimony trioxide, antimony pentasulfide)	–	–	+	+	–	+	Second
Case-control studies							
Longerich et al. 1991 (not reported)	+	–	+	–	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable

*Key question used to assign risk of bias tier

Table B-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects (inhalation only)										
Inhalation acute exposure										
Brieger et al. 1954 (rabbit) (antimony trisulfide)	NA	NA	NA	NA	+	-	**+**	+	NA	Second
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
Price et al. 1979 (rat, stibine)	–	+	+	+	+	+			NA	Second
Price et al. 1979 (guinea pig, stibine)	–	+	+	+	+	+			NA	Second
Inhalation intermediate exposure										
Belyaeva 1967 (rat, antimony trisulfide)	+	+	+	–	+	–	**–**	+	NA	Second
Brieger et al. 1954 (rat, antimony trisulfide)	NA	NA	NA	NA	+	–	**+**	+	NA	Second

Table B-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Dernehl et al. 1945 (guinea pig, antimony trioxide)	–	–	–	–	+	–	–	+	NA	Third
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
Inhalation chronic exposure										
Gross et al. 1952 (rat, antimony trisulfide)	–	+	+	–	+	–	+	+	NA	First
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	+	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	+	–	NA	First
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Watt 1983 (pig, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First

Table B-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Cardiovascular effects(myocardium damage and/or EKG alterations)										
Inhalation acute exposure										
Brieger et al. 1954 (rabbit, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Inhalation intermediate exposure										
Brieger et al. 1954 (rat, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Brieger et al. 1954 (rabbit, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Dernehl et al. 1945 (guinea pig, antimony trioxide)	–	–	–	–	+	–	–	+	NA	Third
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First

Table B-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation chronic exposure										
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	+	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	+	–	NA	First
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Watt 1983 (pigs, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Oral acute exposure										
NTP 1992 (rat, antimony potassium tartrate)	+	+	++	+	++	++	++	++	NA	First
NTP 1992 (mouse, antimony potassium tartrate)	+	+	++	+	++	++	++	++	NA	First

Table B-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Oral intermediate exposure										
Hext et al. 1999 (rat, antimony trioxide)	+	+	+	+	+	++	+	+	NA	First
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	++	+	+	++	+	+	NA	First
Outcome: Gastrointestinal effects										
Inhalation chronic exposure										
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	+	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	+	–	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++		++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Watt 1983 (pig, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Oral acute exposure										
Houpt et al. 1984 (dog, antimony potassium tartrate)	–	+	+	+	+	–	+	+	NA	First

Table B-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
NTP 1992 (rat, antimony potassium tartrate)	+	+	++	+	++	++	++	++	NA	First
NTP 1992 (mouse, antimony potassium tartrate)	+	+	++	+	++	++	++	++	NA	First
Oral intermediate exposure										
Hext et al. 1999 (rat, antimony trioxide)	+	+	+	+	+	++	+	+	+	First
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	+	+	+	+	+	–	NA	First
Outcome: Metabolic effects (altered blood glucose levels)										
Oral intermediate exposure										
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	+	+	+	+	+	–	NA	First
Oral chronic exposure										
Schroeder et al. 1970 (rat, antimony potassium tartrate)	+	+	+	+	+	–	+	–	NA	First

Table B-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Developmental effects										
Inhalation intermediate exposure										
Belyaeva 1967 (rat, antimony trisulfide)	+	+	+	–	+	–	–	+	NA	Second
Oral intermediate exposure										
Angrisani et al. 1988 (rat pup CV, antimony trichloride)	+	+	+	+	+	–	+	+	NA	First
Rossi et al. 1987 (rat, antimony trichloride)	+	+	+	+	+	–	+	+	NA	First
Rossi et al. 1987 (rat pup CV, antimony trichloride)	+	+	+	+	+	–	+	+	NA	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

B.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including DHHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to antimony and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

B.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to antimony and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for observational epidemiology, human-controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human-controlled exposure studies, and experimental animal studies are presented in Tables B-10, B-11, and B-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table B-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table B-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table B-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, cardiovascular, gastrointestinal, metabolic, and developmental effects observed in the observational epidemiology and animal experimental studies are presented in Tables B-13 and B-14, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table B-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table B-15.

Table B-13. Presence of Key Features of Study Design for Antimony—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Cohort studies					
Jones 1994 (antimony metal and antimony trioxide)	No	Yes	Yes	Yes	Moderate
Renes 1953 (antimony oxides)	No	Yes	Yes	No	Low
Schnorr et al. 1995 (antimony oxides)	No	Yes	Yes	Yes	Moderate
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low
Cooper et al. 1968 (antimony trioxide)	No	Yes	Yes	No	Low
Case series					
Potkonjak and Pavlovich 1983 (antimony oxides)	No	Yes	Yes	No	Low
Taylor 1966 (antimony trichloride)	No	Yes	Yes	No	Low
Outcome: Cardiovascular effects					
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low
Outcome: Gastrointestinal effects					
Cohort studies					
Renes 1953 (antimony oxides)	No	Yes	Yes	No	Low
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low
Case series					
Taylor 1966 (antimony trichloride)	No	Yes	Yes	No	Low
Outcome: Developmental effects					
Cohort studies					
Belyaeva 1967 (antimony metal, antimony trioxide, antimony pentasulfide)	No	No	Yes	Yes	Low
Case-control studies					
Longerich et al. 1991 (not reported)	No	No	Yes	Yes	Low

Table B-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Inhalation acute exposure					
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Moderate
NTP 2016 (rat, antimony trioxide)	Yes	No	Yes	Yes	Moderate
NTP 2016 (mouse, antimony trioxide)	Yes	No	Yes	Yes	Moderate
Price et al. 1979 (rat, stibine)	Yes	No	Yes	No	Low
Price et al. 1979 (guinea pig, stibine)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Belyaeva 1967 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Brieger et al. 1954 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Yes	No	Yes	No	Low
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Gross et al. 1952 (rat, antimony trisulfide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	Yes	Yes	High
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (pig, antimony trioxide)	Yes	No	Yes	Yes	Moderate
Outcome: Cardiovascular effects (myocardium damage or altered EKG)					
Inhalation acute exposure					
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Brieger et al. 1954 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Low
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	Yes	No	Yes	No	Low

Table B-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	Yes	No	Yes	No	Low
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Yes	No	Yes	No	Low
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Inhalation chronic exposure					
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	No	Yes	Moderate
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
NTP 2016 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Watt 1983 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Watt 1983 (pigs, antimony trioxide)	Yes	No	Yes	No	Low
Oral acute exposure					
NTP 1992 (rat, antimony potassium tartrate)	Yes	No	No	Yes	Low
NTP 1992 (mouse, antimony potassium tartrate)	Yes	No	No	Yes	Low
Oral intermediate exposure					
Hext et al. 1999 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	No	Yes	Moderate
Outcome: Gastrointestinal effects					
Inhalation chronic exposure					
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	Yes	Yes	High
NTP 2016 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (pig, antimony trioxide)	Yes	No	Yes	Yes	Moderate
Oral acute exposure					
Houpt et al. 1984 (dog, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
NTP 1992 (rat, antimony potassium tartrate)	Yes	No	Yes	Yes	Moderate
NTP 1992 (mouse, antimony potassium tartrate)	Yes	No	Yes	Yes	Moderate

Table B-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral intermediate exposure					
Hext et al. 1999 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Outcome: Metabolic effects (altered blood glucose levels)					
Oral intermediate exposure					
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Oral Chronic exposure					
Schroeder et al. 1970 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Inhalation intermediate exposure					
Belyaeva 1967 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Oral intermediate exposure					
Angrisani et al. 1988 (rat pup CV, antimony trichloride)	Yes	Yes	Yes	Yes	High
Rossi et al. 1987 (rat, antimony trichloride)	Yes	Yes	Yes	Yes	High
Rossi et al. 1987 (rat pup CV, antimony trichloride)	Yes	Yes	Yes	Yes	High

Table B-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Studies finding effects		
Inhalation acute exposure		
Animal studies		
Brieger et al. 1954 (rabbit, antimony trisulfide)	Moderate	
NTP 2016 (rat, antimony trioxide)	Moderate	
NTP 2016 (mouse, antimony trioxide)	Moderate	Moderate
Price et al. 1979 (rat, stibine)	Low	
Price et al. 1979 (guinea pig, stibine)	Low	
Inhalation intermediate exposure		
Animal studies		
Belyaeva 1967 (rat, antimony trisulfide)	Moderate	
Brieger et al. 1954 (rat, antimony trisulfide)	Moderate	High
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Low	
Newton et al. 1994 (rat, antimony trioxide)	High	
Inhalation chronic exposure		
Human studies		
Renes 1953 (antimony oxides)	Low	
Schnorr et al. 1995 (antimony oxides)	Moderate	
Cooper et al. 1968 (antimony trioxide)	Low	Moderate
Potkonjak and Pavlovich 1983 (antimony oxides)	Low	
Taylor 1966 (antimony trichloride)	Low	
Animal studies		
Gross et al. 1952 (rat, antimony trisulfide)	High	
Groth et al. 1986 (rat, antimony trioxide)	High	
Groth et al. 1986 (rat, antimony ore)	High	
Newton et al. 1994 (rat, antimony trioxide)	High	High
NTP 2016 (rat, antimony trioxide)	High	
NTP 2016 (mouse, antimony trioxide)	High	
Watt 1983 (rat, antimony trioxide)	High	
Watt 1983 (pig, antimony trioxide)	Moderate	
Studies finding no effects		
Inhalation chronic exposure		
Human studies		
Brieger et al. 1954 (antimony trisulfide)	Low	
Jones 1994 (antimony metal and antimony trioxide)	Moderate	Moderate

Table B-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Outcome: Cardiovascular effects					
Studies finding effects on myocardium and/or EKGs					
Inhalation acute exposure					
Animal studies					
Brieger et al. 1954 (rabbit, antimony trisulfide)		Low		Low	
Inhalation intermediate exposure					
Animal studies					
Brieger et al. 1954 (rat, antimony trisulfide)		Moderate			
Brieger et al. 1954 (rabbit, antimony trisulfide)		Low		Moderate	
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)		Low			
Inhalation chronic exposure					
Human studies					
Brieger et al. 1954 (antimony trisulfide)		Low		Low	
Studies finding no effects on myocardium and/or EKGs					
Inhalation intermediate exposure					
Animal studies					
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)		Low			
Dernehl et al. 1945 (guinea pig, antimony trioxide)		Low		Moderate	
Newton et al. 1994 (rat, antimony trioxide)		Moderate			
Inhalation chronic exposure					
Animal studies					
Groth et al. 1986 (rat, antimony trioxide)		Moderate			
Groth et al. 1986 (rat, antimony ore)		Moderate			
Newton et al. 1994 (rat, antimony trioxide)		Moderate			
NTP 2016 (rat, antimony trioxide)		Moderate		Moderate	
NTP 2016 (mouse, antimony trioxide)		Moderate			
Watt 1983 (rat, antimony trioxide)		Moderate			
Watt 1983 (pigs, antimony trioxide)		Low			

Table B-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral acute exposure					
Animal studies					
NTP 1992 (rat, antimony potassium tartrate)		Low		Low	
NTP 1992 (mouse, antimony potassium tartrate)		Low			
Oral intermediate exposure					
Animal studies					
Hext et al. 1999 (rat, antimony trioxide)		Moderate		Moderate	
Poon et al. 1998 (rat, antimony potassium tartrate)		Moderate			
Outcome: Gastrointestinal effects					
Studies finding effects					
Inhalation chronic exposure					
Human studies					
Brieger et al. 1954		Low			
Renes 1953		Low		Low	
Taylor 1966		Low			
Animal studies					
NTP 2016 (mouse, antimony trioxide)		High		High	
Oral acute exposure					
Animal studies					
Houpt et al. 1984 (dog, antimony potassium tartrate)		High		High	
NTP 1992 (mouse, antimony potassium tartrate)		Moderate			
Studies finding no effects					
Inhalation chronic exposure					
Animal studies					
Groth et al. 1986 (rat, antimony trioxide)		High			
Groth et al. 1986 (rat, antimony ore)		High			
NTP 2016 (rat, antimony trioxide)		High		High	
Watt 1983 (rat, antimony trioxide)		High			
Watt 1983 (pig, antimony trioxide)		Moderate			

Table B-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral acute exposure					
Animal studies					
NTP 1992 (rat, antimony potassium tartrate)		Moderate		Moderate	
Oral intermediate exposure					
Animal studies					
Hext et al. 1999 (rat, antimony trioxide)		High		High	
Poon et al. 1998 (rat, antimony potassium tartrate)		High			
Outcome: Metabolic effects					
Studies finding effects on serum glucose levels					
Oral intermediate exposure					
Animal studies					
Poon et al. 1998 (rat, antimony potassium tartrate)		High		High	
Oral chronic exposure					
Animal studies					
Schroeder et al. 1970 (rat, antimony potassium tartrate)		High		High	
Outcome: Developmental effects					
Studies finding effects					
Inhalation intermediate exposure					
Animal studies					
Belyaeva 1967 (rat, antimony trisulfide)		Moderate		Moderate	
Inhalation chronic exposure					
Human studies					
Belyaeva 1967 (metallic antimony, antimony trioxide, antimony pentasulfide)		Low		Low	
Oral intermediate exposure					
Animal studies					
Angrisani et al. 1988 (rat, pup CV, antimony trichloride)		High			
Rossi et al. 1987 (rat, pup CV, antimony trichloride)		High		High	
Rossi et al. 1987 (rat, antimony trichloride)		High			

Table B-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Studies finding no effects					
Inhalation chronic exposure					
Human studies					
Longerich et al. 1991 (not reported)		Low		Low	

B.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, cardiovascular, gastrointestinal, metabolic, and developmental effects are presented in Table B-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with antimony exposure is presented in Table B-17.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables B-8 and B-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
  - No downgrade if most studies are in the risk of bias first tier
  - Downgrade one confidence level if most studies are in the risk of bias second tier
  - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
  - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
  - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect

- Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
  - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
  - Directness of the end points to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
  - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
  - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
  - No downgrade if none of the factors are considered indirect
  - Downgrade one confidence level if one of the factors is considered indirect
  - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
  - No downgrade if there are no serious imprecisions
  - Downgrade one confidence level for serious imprecisions
  - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

Table B-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Studies finding effects			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	+1 magnitude, +1 consistency	High
Studies finding no effects			
Human studies	Moderate	-1 risk of bias,	Low
Outcome: Cardiovascular effects			
Studies finding effects on myocardium and/or EKGs			
Human studies	Low	-1 risk of bias,	Very low
Animal studies	Moderate	-1 risk of bias	Low
Studies finding no effects on myocardium and/or EKGs			
Animal studies	Moderate	None	Moderate
Outcome: Gastrointestinal effects			
Studies finding effects			
Human studies	Low	-1 risk of bias	Very low
Animal studies	High	None	High
Studies finding no effects			
Animal studies	High	None	High
Outcome: Metabolic effects			
Studies finding effects on serum glucose levels			
Animal studies	High	None	High
Outcome: Developmental effects			
Studies finding effects			
Human studies	Low	-1 risk of bias	Very low
Animal studies	High	None	High
Studies finding no effects			
Human studies	Low	-1 risk of bias	Very low

Table B-17. Confidence in the Body of Evidence for Antimony

Outcome	Confidence in body of evidence	
	Human studies	Animal studies
Respiratory effects		
Effect	Low	High
No effect	Low	No data
Cardiovascular effects		
Effects on myocardium/EKG	Very low	Low
No effect on myocardium/EKG	No data	Moderate
Gastrointestinal effects		
Effect	Very low	High
No effect	No data	High
Metabolic effects		
Effect	No data	High
No effect	No data	No data
Developmental effects		
Effect	Very low	High
No effect	Very low	No data

B.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for antimony, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome or very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for antimony is presented in Table B-18.

Table B-18. Level of Evidence of Health Effects for Antimony

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation only)			
	Low	Health effect	Low
	Low	No effect	Inadequate
Cardiovascular—myocardial and EKG alterations			
	Very Low	Health effect	Inadequate
Gastrointestinal effect			
	Very Low	Health effect	Inadequate
Metabolic—serum glucose alterations			
	No data	–	No data
Developmental effects			
	Very Low	Health effect	Inadequate
Animal studies			
Respiratory effects (inhalation only)			
	High	Health effect	High
Cardiovascular—myocardial and EKG alterations			
	Low	Health effect	Low
	Moderate	No effect	Inadequate
Gastrointestinal effects			
	High	Health effect	High
	High	No effect	Evidence of no health effect
Metabolic—serum glucose alterations			
	High	Health effect	High
Developmental effects			
	High	Health effect	High
	No data	-	No data

B.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

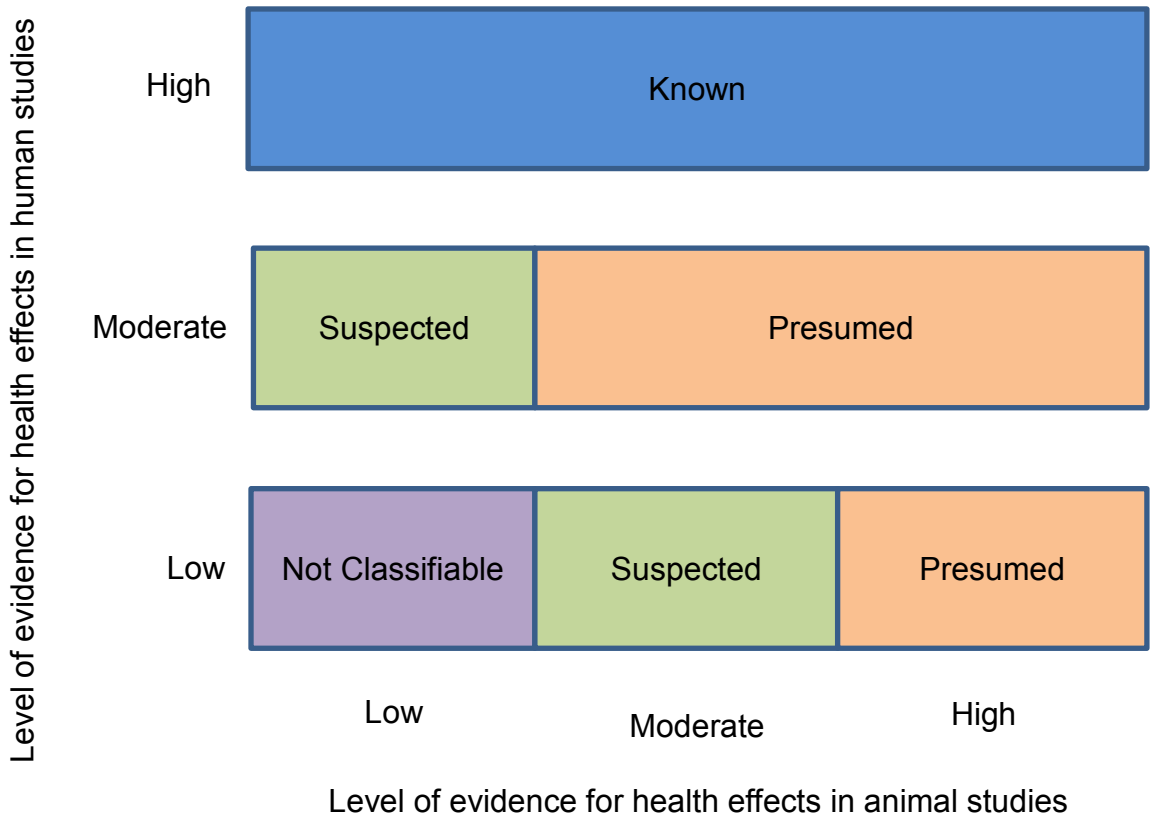
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing

evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure B-2 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure B-2. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for antimony are listed below and summarized in Table B-19.

Presumed Health Effects

- Respiratory effects following inhalation exposure
    - Low evidence from studies of antimony workers (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Renes 1953; Schnorr et al. 1995; Taylor 1966).
    - High level of evidence in rats, mice, rabbits, guinea pigs, and pigs from acute exposure to antimony trisulfide, antimony trioxide, and stibine (Brieger et al. 1954; NTP 2016; Price et al. 1979), intermediate exposure to antimony trisulfide and antimony trioxide (Belyaeva 1967; Brieger et al. 1954; Dernehl et al. 1945; Newton et al. 1994), and chronic exposure to antimony trisulfide, antimony trioxide, and antimony ore (Gross et al. 1952; Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983).
- Gastrointestinal effects
    - Inadequate evidence from studies of antimony workers (Brieger et al. 1954; Renes 1953; Taylor et al. 1966).
    - High level of evidence for gastrointestinal irritation in dogs (Houpt et al. 1984) and mice (NTP 1992, 2016). Inhalation and oral studies in rats with initial confidences of high or moderate did not find histological alterations in the gastrointestinal tract following inhalation exposure to antimony trioxide (Groth et al. 1986; NTP 2016; Watt 1983) or antimony ore (Groth et al. 1986) or oral exposure to antimony trioxide (Hext et al. 1999) or antimony potassium tartrate (NTP 1992; Poon et al. 1998).

Suspected Health Effects

- Cardiovascular-myocardial and EKG alterations
    - Inadequate evidence in humans exposed to antimony trisulfide (Brieger et al. 1954)
    - Low evidence in rats, rabbits, and dogs exposed via inhalation to antimony trisulfide (Brieger et al. 1954) and in rats exposed to antimony potassium tartrate (Schroeder et al. 1970). No myocardial alterations were observed in rat, mouse, pig, or guinea pig antimony ore or antimony trioxide inhalation studies with initial moderate confidence levels (Dernehl et al. 1945; Groth et al. 1986; Newton et al. 1994; Watt 1983) or in antimony trioxide and antimony potassium tartrate oral studies with initial moderate confidence level (Hext et al. 1999; NTP 1992; Poon et al. 1998).
    - Although the hazard identification for myocardial and EKG alterations should be not classifiable based on inadequate evidence in humans and low evidence in animals, the level of the hazard identification was raised to suspected health effect based on consistent evidence of EKG alterations in patients treated with injected trivalent or pentavalent antimony compounds (Dancaster et al. 1966; Honey 1960; Lawn et al. 2006; Neves et al. 2009; Sundar et al. 1998; Thakur 1998) and in animal studies involving parenteral

administration (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966).

- Metabolic effect (decreases in blood glucose levels)
  - No data are available on whether inhalation, oral, or dermal exposure to antimony alters blood glucose levels in humans.
  - High evidence in animal studies based on two studies that found decreases in blood glucose levels following intermediate (Poon et al. 1998) or chronic (Schroeder et al. 1970) oral exposure. Decreases in blood glucose levels were also found in rats following repeated intramuscular injection of two organic pentavalent compounds (Alkhawajah et al. 1992b).
  - Based on the high evidence found in the two animal studies, decreases in blood glucose levels should be classified as a presumed health effect. However, because blood glucose levels have only been assessed in two studies administering antimony via environmentally relevant routes of exposure, the hazard identification was downgraded to suspected health effect.
- Developmental effects
  - Inadequate evidence of developmental effects (decreases in infant growth) from an occupational exposure study (Belyaeva 1976).
  - High evidence of developmental toxicity from animal studies. An inhalation study found decreases in the number of offspring in rats exposed to antimony trioxide during gestation (Belyaeva 1967). An antimony trichloride oral exposure study found decreases in postnatal growth resulting from gestation and lactation exposure, but no effect on the number of offspring or abnormalities (Rossi et al. 1987).
  - Decreases in birth weight and decreases in the number of viable offspring were observed in rat studies involving gestation and/or lactation exposure to subcutaneously administered meglumine antimoniate (Coelho et al. 2014a; Miranda et al. 2006) or intramuscularly administered sodium stibogluconate, meglumine antimoniate, or antimony trichloride (Alkhawajah et al. 1992a).
  - Although the hazard identification for developmental effects, particularly for decreased growth, should be presumed health effect based on inadequate evidence in humans and high evidence in humans, the hazard identification was lowered to suspected health effect based on the small number of studies evaluating the developmental toxicity of antimony by environmentally relevant routes of exposure.

Table B-19. Hazard Identification Conclusions for Antimony

Outcome	Hazard identification
Respiratory effects	Presumed health effect following inhalation exposure
Cardiovascular-myocardial and EKG alterations	Suspected health effect following exposure to soluble antimony compounds
Gastrointestinal effects	Presumed health effect
Metabolic effects (decreased serum glucose levels)	Suspected health effect
Developmental effects	Suspected health effect

This page is intentionally blank.

APPENDIX C. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page C-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures include death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page C-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

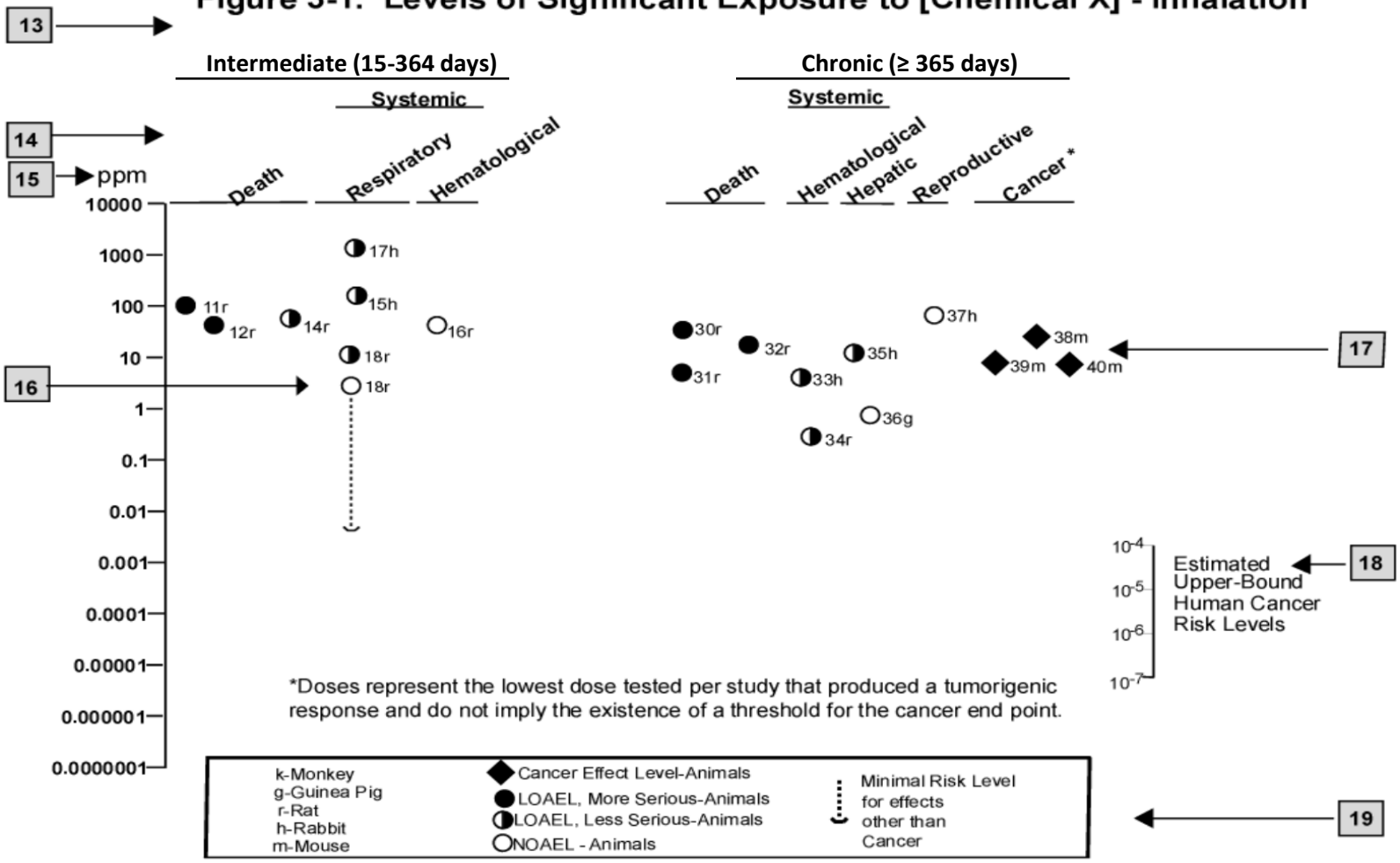
	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.

[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



This page is intentionally blank.

APPENDIX D. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

APPENDIX D

DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level

MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell

WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result